Paula Dor

Spivack 10_730704 - - History

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=> d his ful

     (FILE 'HOME' ENTERED AT 11:03:51 ON 03 AUG 2006)

     FILE 'REGISTRY' ENTERED AT 11:04:43 ON 03 AUG 2006
L1             1 SEA ABB=ON  PLU=ON  "AM 251 (PHARMACEUTICAL)"/CN
L2             1 SEA ABB=ON  PLU=ON  "L 796568"/CN
L3             1 SEA ABB=ON  PLU=ON  PHENTERMINE/CN
L4            48 SEA ABB=ON  PLU=ON  PHENTERMINE NOT L3
L5             1 SEA ABB=ON  PLU=ON  THEOPHYLLINE/CN
L6          2785 SEA ABB=ON  PLU=ON  THEOPHYLLINE
L7          2784 SEA ABB=ON  PLU=ON  L6 NOT L5
L8             1 SEA ABB=ON  PLU=ON  ORLISTAT/BI

     FILE 'HCAPLUS' ENTERED AT 11:09:42 ON 03 AUG 2006

     FILE 'REGISTRY' ENTERED AT 11:10:29 ON 03 AUG 2006
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L9              SEL PLU=ON  L1 1- CHEM :        3 TERMS
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     FILE 'HCAPLUS' ENTERED AT 11:10:29 ON 03 AUG 2006
L10          127 SEA ABB=ON  PLU=ON  L9
L11          196 SEA ABB=ON  PLU=ON  L10 OR AM251 OR AM(W)251

     FILE 'REGISTRY' ENTERED AT 11:10:54 ON 03 AUG 2006
                SET SMARTSELECT ON
L12             SEL PLU=ON  L3 1- CHEM :       21 TERMS
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     FILE 'HCAPLUS' ENTERED AT 11:10:55 ON 03 AUG 2006
L13         1053 SEA ABB=ON  PLU=ON  L12
L14         1862 SEA ABB=ON  PLU=ON  L13 OR L4 OR ?PHENTERMINE?

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L15             SEL PLU=ON  L2 1- CHEM :        2 TERMS
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     FILE 'HCAPLUS' ENTERED AT 11:12:12 ON 03 AUG 2006
L16             6 SEA ABB=ON  PLU=ON  L15
L17             6 SEA ABB=ON  PLU=ON  L16 OR L796568 OR "L"(W)796568

     FILE 'REGISTRY' ENTERED AT 11:13:13 ON 03 AUG 2006
                SET SMARTSELECT ON
L18             SEL PLU=ON  L8 1- CHEM :        7 TERMS
                SET SMARTSELECT OFF

     FILE 'HCAPLUS' ENTERED AT 11:13:13 ON 03 AUG 2006
L19          673 SEA ABB=ON  PLU=ON  L18
L20          673 SEA ABB=ON  PLU=ON  L19 OR ?ORLISTAT?

     FILE 'REGISTRY' ENTERED AT 11:13:53 ON 03 AUG 2006
                SET SMARTSELECT ON
L21             SEL PLU=ON  L5 1- CHEM :       91 TERMS
                SET SMARTSELECT OFF

     FILE 'HCAPLUS' ENTERED AT 11:16:50 ON 03 AUG 2006
L22         26148 SEA ABB=ON  PLU=ON  L21
L23         48194 SEA ABB=ON  PLU=ON  L22 OR L7 OR ?THEOPHYLLIN?
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L24           3 SEA ABB=ON  PLU=ON  L11 AND L14
L25           0 SEA ABB=ON  PLU=ON  L11 AND L17
L26           2 SEA ABB=ON  PLU=ON  L11 AND L20
L27           0 SEA ABB=ON  PLU=ON  L17 AND (L23 OR L20)
L28           4 SEA ABB=ON  PLU=ON  L24 OR L25 OR L26 OR L27
                D STAT QUE
                D IBIB ABS HITSTR L28 1-4
L38         105 SEA ABB=ON  PLU=ON  ("NARGUND R"/AU OR "NARGUND R P"/AU OR
                "NARGUND RAVI"/AU OR "NARGUND RAVI P"/AU OR "NARGUND RAVI
                PANDURANG"/AU)
L39          82 SEA ABB=ON  PLU=ON  ("VAN DER PLOEG L"/AU OR "VAN DER PLOEG L
                H T"/AU OR "VAN DER PLOEG L H Y"/AU OR "VAN DER PLOEG LENONARDU
                S H T"/AU OR "VAN DER PLOEG LEONARDUS"/AU OR "VAN DER PLOEG
                LEONARDUS H T"/AU)
L40         102 SEA ABB=ON  PLU=ON  FONG T/AU OR FONG T M/AU OR "FONG TUNG"/AU
                OR ("FONG TUNG M"/AU OR "FONG TUNG MING"/AU)
L41          90 SEA ABB=ON  PLU=ON  "MACNEIL D"/AU OR "MACNEIL D J"/AU OR
                ("MACNEIL DOUGLAS"/AU OR "MACNEIL DOUGLAS J"/AU OR "MACNEIL
                DOUGLAS JOHN"/AU)
L42        1474 SEA ABB=ON  PLU=ON  "CHEN HOWARD"/AU OR ("CHEN HOWARD Y"/AU OR
                "CHEN HOWARD YONG WEN"/AU) OR CHEN H/AU OR CHEN H Y/AU
L43          81 SEA ABB=ON  PLU=ON  "MARSH DONALD"/AU OR "MARSH DOUGLAS G"/AU
                OR "MARSH DONALD"/AU OR "MARSH DONALD J"/AU
L44          23 SEA ABB=ON  PLU=ON  ("WARMKE J W"/AU OR "WARMKE JEFFREY"/AU OR
                "WARMKE JEFFREY W"/AU OR "WARMKE JEFFREY WAYNE"/AU)
L45          14 SEA ABB=ON  PLU=ON  (L38 OR L39 OR L40 OR L41 OR L42 OR L43 OR
                L44) AND (L11 OR L14 OR L17 OR L20 OR L23)
L46           1 SEA ABB=ON  PLU=ON  L38 AND L39 AND L40 AND L41 AND L42 AND
                L43 AND L44
L47          21 SEA ABB=ON  PLU=ON  L38 AND (L39 OR L40 OR L41 OR L42 OR L43
                OR L44)
L48          41 SEA ABB=ON  PLU=ON  L39 AND (L40 OR L41 OR L42 OR L43 OR L44)
L49          11 SEA ABB=ON  PLU=ON  L40 AND (L41 OR L42 OR L43 OR L44)
L50           8 SEA ABB=ON  PLU=ON  L41 AND (L42 OR L43 OR L44)
L51           8 SEA ABB=ON  PLU=ON  L42 AND (L43 OR L44)
L52           1 SEA ABB=ON  PLU=ON  (L43 AND L44)
                D STAT QUE L45
                D IBIB ABS HITSTR L45 1-14
L53          62 SEA ABB=ON  PLU=ON  (L46 OR L47 OR L48 OR L49 OR L50 OR L51 OR
                L52) NOT (L28 OR L45)
                D STAT QUE L53
                D IBIB ABS HITSTR L53 1-62


FILE HOME

FILE REGISTRY
Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:     1 AUG 2006  HIGHEST RN 897851-29-5
DICTIONARY FILE UPDATES:    1 AUG 2006  HIGHEST RN 897851-29-5

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH January 6, 2006

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.
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REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

FILE HCAPLUS

FILE COVERS 1907 - 3 Aug 2006 VOL 145 ISS 6
FILE LAST UPDATED: 1 Aug 2006 (20060801/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=>

TI THE CANNABINOID LIGAND AM251 ACTS As AN INVERSE AGONIST AT THE CB1 RECEPTOR IN VITRO, AND INDUCES WEIGHT LOSS IN CAFETERIA DIET - FED MICE IN VIVO.

AU Hjorth, S. [Reprint Author]; Johansson, M. S. [Reprint Author]; Carlsson, K.; Greasley, P. J.

CS Integrative Pharmacology, AstraZeneca R and D, Molndal, Molndal, Sweden

SO Society for Neuroscience Abstract Viewer and Itinerary Planner, (2002) Vol. 2002, pp. Abstract No. 775.17. http://sfn.scholarone.com. cd-rom. Meeting Info.: 32nd Annual Meeting of the Society for Neuroscience. Orlando, Florida, USA. November 02-07, 2002. Society for Neuroscience.

DT Conference; (Meeting)
Conference; (Meeting Poster)
Conference; Abstract; (Meeting Abstract)

LA English

ED Entered STN: 16 Jul 2003
Last Updated on STN: 16 Jul 2003

AB AM251 is a close structural (4-iodophenyl) analogue to the reference CB1 receptor inverse agonist SR141716 and is frequently used as an antagonist at the CB1 sites. The present study assessed i) whether the drug is indeed a true CB1 receptor antagonist and, given central CB1 receptor modulation of food intake, ii) if its sub-chronic administration would induce weight loss in obese mice. AM251 was compared with SR141716 with regard to its ability to inhibit GTPgammaS binding mediated by CB1 receptors expressed in HEK293 cells in vitro, and to reduce body weight in cafeteria diet-fed mice. AM251 was approximately 3x less potent than SR141716 (IC50 6.4 and 1.8 nM, respectively) in the GTPgammaS assay, and both agents demonstrated equivalent inverse agonist properties. In vivo, 7 days administration of AM251 or SR141716 (10mg/kg i.p. once daily) resulted in a significant drop in body weight of about 8% from baseline (despite continued access to palatable diet). The response to both compounds in this regard was virtually superimposable. For comparison, untreated and vehicle animals gained apprx5% weight over the same time period. We conclude that AM251 is not an antagonist but rather an inverse agonist at CB1 receptors, displaying slightly lower potency than, but similar efficacy to SR141716. Moreover, both agents induced clear-cut weight loss in cafeteria diet-induced obese mice, thus concurring with the notion that inverse agonism at (central) CB1 receptors affects appetite and/or reward mechanisms and may represent an important exploitable target in the development of novel anti-obesity treatments.

AB. . . antagonist and, given central CB1 receptor modulation of food intake, ii) if its sub-chronic administration would induce weight loss in obese mice. AM251 was compared with SR141716 with regard to its ability to inhibit GTPgammaS binding mediated by CB1 receptors expressed. . . displaying slightly lower potency than, but similar efficacy to SR141716. Moreover, both agents induced clear-cut weight loss in cafeteria diet-induced obese mice, thus concurring with the notion that inverse agonism at (central) CB1 receptors affects appetite and/or reward mechanisms and may represent an important exploitable target in the development of novel anti-obesity treatments.

IT Major Concepts
Behavior; Nutrition; Pharmacology

IT Diseases
obesity: nutritional disease
Obesity (MeSH)

IT Chemicals & Biochemicals
AM251: anorexic-drug, cannabinoid ligand; CB1 receptor; SR14176

RN 51709-03-6Q (AM251)
183232-66-8Q (AM251)

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=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 11:16:50 ON 03 AUG 2006
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2006 AMERICAN CHEMICAL SOCIETY (ACS)
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FILE COVERS 1907 - 3 Aug 2006  VOL 145 ISS 6
FILE LAST UPDATED: 1 Aug 2006  (20060801/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

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=> d stat que
L1             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "AM 251 (PHARMACEUTICAL)"/CN

L2             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "L 796568"/CN
L3             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  PHENTERMINE/CN
L4            48 SEA FILE=REGISTRY ABB=ON  PLU=ON  PHENTERMINE NOT L3
L5             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  THEOPHYLLINE/CN
L6          2785 SEA FILE=REGISTRY ABB=ON  PLU=ON  THEOPHYLLINE
L7          2784 SEA FILE=REGISTRY ABB=ON  PLU=ON  L6 NOT L5
L8             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  ORLISTAT/BI
L9               SEL  PLU=ON  L1 1- CHEM :        3 TERMS
L10          127 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L9
L11          196 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L10 OR AM251 OR AM(W)251
L12              SEL  PLU=ON  L3 1- CHEM :       21 TERMS
L13         1053 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L12
L14         1862 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L13 OR L4 OR ?PHENTERMINE?
L15              SEL  PLU=ON  L2 1- CHEM :        2 TERMS
L16            6 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L15
L17            6 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L16 OR L796568 OR "L"(W)796568

L18              SEL  PLU=ON  L8 1- CHEM :        7 TERMS
L19          673 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L18
L20          673 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L19 OR ?ORLISTAT?
L21              SEL  PLU=ON  L5 1- CHEM :       91 TERMS
L22        26148 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L21
L23        48194 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L22 OR L7 OR ?THEOPHYLLIN?
L24            3 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L11 AND L14
L25            0 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L11 AND L17
L26            2 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L11 AND L20
L27            0 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L17 AND (L23 OR L20)
L28            4 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L24 OR L25 OR L26 OR L27
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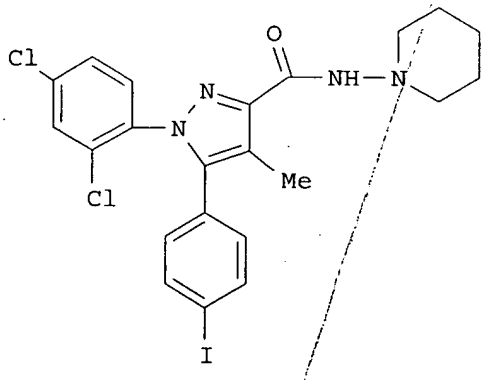
=> d ibib abs hitstr l28 1-4

L28 ANSWER 1 OF 4 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:317218 HCAPLUS
DOCUMENT NUMBER: 144:363116
TITLE: Combination therapy comprising PYY agonists for the treatment of obesity
INVENTOR(S): Amatruda, John M.; Daruwala, Paul; Erondu, Ngozi E.; Macneil, Douglas J.; Moller, David E.; Qian, Su
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 99 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006036770	A2	20060406	WO 2005-US34096	20050922

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2004-612657P P 20040924
OTHER SOURCE(S): MARPAT 144:363116
GI



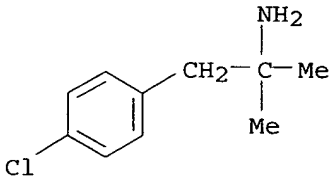
I

AB The present invention relates to compns. comprising PYY, PYY3-36, or a PYY agonist, and an anti-obesity agent, useful for the treatment and prevention of obesity and obesity-related disorders. The present

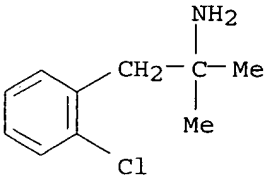
invention further relates to methods of treating or preventing obesity and obesity-related disorder in a subject in need thereof by administering a composition of the present invention. One example is a in vivo study of the effect of PYY3-36 on 4 h and 16 h food intake and body weight gain in mice and another example is an in vivo study of the effect of the combination of PYY3-36 and CB-1 inverse agonist AM-251 (I) on food intake and body weight in mice.

IT 461-78-9, Chlorphentermine 10389-73-8, Clortermine
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(PPY agonist; combination therapy comprising PYY agonists for the treatment of obesity)

RN 461-78-9 HCAPLUS
CN Benzeneethanamine, 4-chloro-α,α-dimethyl- (9CI) (CA INDEX NAME)

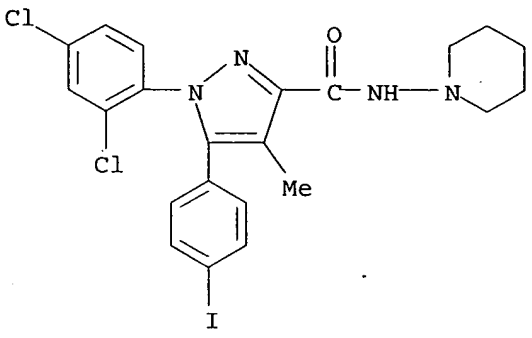


RN 10389-73-8 HCAPLUS
CN Benzeneethanamine, 2-chloro-α,α-dimethyl- (9CI) (CA INDEX NAME)



IT 183232-66-8, AM-251
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination therapy comprising PYY agonists for the treatment of obesity)

RN 183232-66-8 HCAPLUS
CN 1H-Pyrazole-3-carboxamide, 1-(2,4-dichlorophenyl)-5-(4-iodophenyl)-4-methyl-N-1-piperidinyl- (9CI) (CA INDEX NAME)



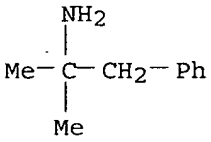
L28 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:147251 HCAPLUS
DOCUMENT NUMBER: 144:219280
TITLE: Combination of bupropion and a second compound for affecting weight loss
INVENTOR(S): Weber, Eckard; Cowley, Michael Alexander
PATENT ASSIGNEE(S): Orexigen Therapeutics, Inc., USA
SOURCE: PCT Int. Appl., 35 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006017504	A1	20060216	WO 2005-US27424	20050801
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
US 2006058293	A1	20060316	US 2005-194201	20050801
PRIORITY APPLN. INFO.:			US 2004-598558P	P 20040803

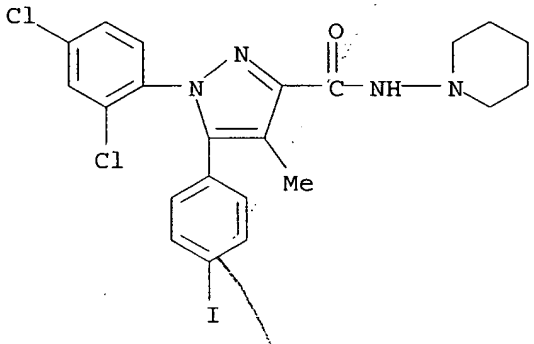
AB Disclosed are compns. for affecting weight loss comprising bupropion and a second compound, where the second compound causes increased agonism of a melanocortin 3 receptor (MC3-R) or a melanocortin 4 receptor (MC4-R) compared to normal physiol. conditions, antagonizes cannabinoid receptor activity, or is useful in the treatment of bipolar disorders.. Also disclosed are methods of affecting weight loss, increasing energy expenditure, increasing satiety in an individual, or suppressing the appetite of an individual, comprising identifying an individual in need thereof and treating that individual with a combination of bupropion and a compound that enhances α-MSH activity, antagonizes cannabinoid receptor activity, or is useful in the treatment of bipolar disorders.
IT 122-09-8, Phentermine 183232-66-8, Am251

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(bupropion combinations for effecting weight loss)

RN 122-09-8 HCAPLUS
CN Benzeneethanamine, α,α-dimethyl- (9CI) (CA INDEX NAME)



RN 183232-66-8 HCAPLUS
CN 1H-Pyrazole-3-carboxamide, 1-(2,4-dichlorophenyl)-5-(4-iodophenyl)-4-methyl-N-1-piperidinyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:395099 HCAPLUS
DOCUMENT NUMBER: 142:423874
TITLE: Combination treatment of obesity involving selective CB1 antagonists and lipase inhibitors
INVENTOR(S): Antel, Jochen; Gregory, Peter-Colin; Krause, Gunter
PATENT ASSIGNEE(S): Solvay Pharmaceuticals GmbH, Germany
SOURCE: PCT Int. Appl., 39 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005039579	A1	20050506	WO 2004-EP52643	20041022

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,

AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2543197	AA	20050506	CA 2004-2543197	20041022
EP 1680116	A1	20060719	EP 2004-791298	20041022

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK

PRIORITY APPLN. INFO.:	EP 2003-103962	A	20031024
	US 2003-513996P	P	20031027
	WO 2004-EP52643	W	20041022

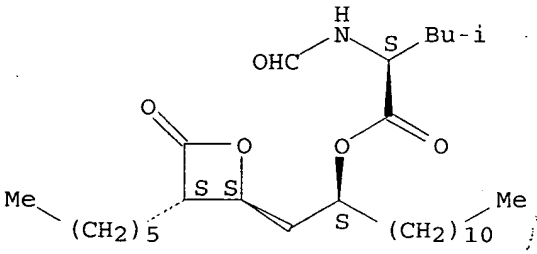
AB The invention discloses the medical use of selective CB1 receptor antagonist compds. in combination with lipase inhibitors. The CB1 antagonists are particularly suitable in combination with lipase inhibitors in the manufacture of medicaments for the treatment and/or prophylaxis of obesity in adolescent or in juvenile patients and/or for the treatment and/or prophylaxis of drug-induced obesity in juvenile as well as in adolescent patients. Preferred lipase inhibitors are orlistat, panclicins, ATL-962 and/or lipstatin.

IT 96829-58-2, Orlistat 183232-66-8, AM 251
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(CB antagonist-lipase inhibitor combination for obesity treatment)

RN 96829-58-2 HCAPLUS

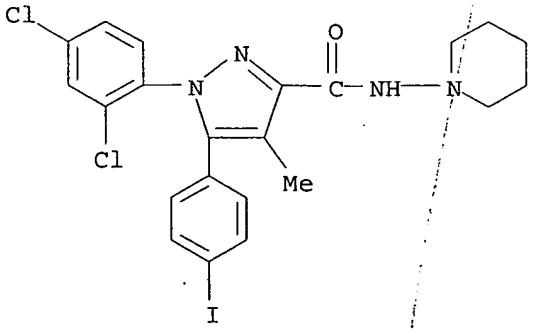
CN L-Leucine, N-formyl-, (1S)-1-[[(2S,3S)-3-hexyl-4-oxo-2-oxetanyl]methyl]dodecyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 183232-66-8 HCAPLUS

CN 1H-Pyrazole-3-carboxamide, 1-(2,4-dichlorophenyl)-5-(4-iodophenyl)-4-methyl-N-1-piperidinyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

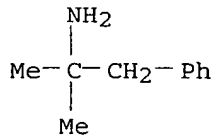
L28 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:513332 HCAPLUS
DOCUMENT NUMBER: 141:47361
TITLE: Combination therapy using an appetite suppressant and/or a metabolic rate enhancer and/or a nutrient absorption inhibitor for the treatment of obesity and obesity-related disorders
INVENTOR(S): Nargund, Ravi P.; Van der Ploeg, Leonardus H. T.; Fong, Tung M.; MacNeil, Douglas J.; Chen, Howard Y.; Marsh, Donald J.; Warmke, Jeffrey
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 43 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004122033	A1	20040624	US 2003-730704	20031208
PRIORITY APPLN. INFO.:			US 2002-432063P	P 20021210

AB The invention discloses compns. comprising an appetite suppressant and/or a metabolic rate enhancer and/or a nutrient absorption inhibitor useful for the treatment of obesity, and obesity-related disorders. The invention also discloses methods for treating or preventing obesity and obesity-related disorders in a subject in need thereof by administering a composition of the invention. The invention further discloses pharmaceutical compns., medicaments, and kits useful in carrying out the methods. Preparation of 11β-hydroxysteroid dehydrogenase 1 inhibitors is included.

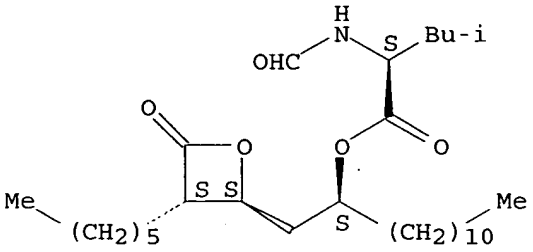
IT 122-09-8, Phentermine 96829-58-2, Orlistat 183232-66-8, AM 251
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(appetite suppressant and/or metabolic rate enhancer and/or nutrient absorption inhibitor for treatment of obesity and obesity-related disorders)

RN 122-09-8 HCAPLUS
CN Benzeneethanamine, α,α-dimethyl- (9CI) (CA INDEX NAME)

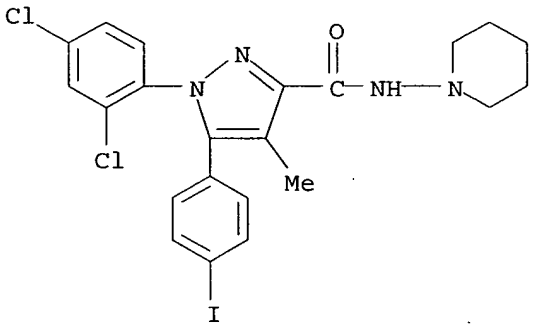


RN 96829-58-2 HCAPLUS
CN L-Leucine, N-formyl-, (1S)-1-[[(2S,3S)-3-hexyl-4-oxo-2-oxetanyl]methyl]dodecyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 183232-66-8 HCAPLUS
CN 1H-Pyrazole-3-carboxamide, 1-(2,4-dichlorophenyl)-5-(4-iodophenyl)-4-methyl-N-1-piperidinyl- (9CI) (CA INDEX NAME)



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L2             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "L 796568"/CN
L3             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  PHENTERMINE/CN
L4            48 SEA FILE=REGISTRY ABB=ON  PLU=ON  PHENTERMINE NOT L3
L5             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  THEOPHYLLINE/CN
L6          2785 SEA FILE=REGISTRY ABB=ON  PLU=ON  THEOPHYLLINE
L7          2784 SEA FILE=REGISTRY ABB=ON  PLU=ON  L6 NOT L5
L8             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  ORLISTAT/BI
L9               SEL  PLU=ON  L1 1- CHEM :        3 TERMS
L10          127 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L9
L11          196 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L10 OR AM251 OR AM(W)251
L12              SEL  PLU=ON  L3 1- CHEM :       21 TERMS
L13         1053 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L12
L14         1862 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L13 OR L4 OR ?PHENTERMINE?
L15              SEL  PLU=ON  L2 1- CHEM :        2 TERMS
L16            6 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L15
L17            6 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L16 OR L796568 OR "L"(W)796568

L18              SEL  PLU=ON  L8 1- CHEM :        7 TERMS
L19          673 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L18
L20          673 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L19 OR ?ORLISTAT?
L21              SEL  PLU=ON  L5 1- CHEM :       91 TERMS
L22        26148 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L21
L23        48194 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L22 OR L7 OR ?THEOPHYLLIN?
L38          105 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ("NARGUND R"/AU OR "NARGUND R
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P"/AU OR "NARGUND RAVI"/AU OR "NARGUND RAVI P"/AU OR "NARGUND RAVI PANDURANG"/AU)

L39 82 SEA FILE=HCAPLUS ABB=ON PLU=ON ("VAN DER PLOEG L"/AU OR "VAN DER PLOEG L H T"/AU OR "VAN DER PLOEG L H Y"/AU OR "VAN DER PLOEG LENONARDUS H T"/AU OR "VAN DER PLOEG LEONARDUS"/AU OR "VAN DER PLOEG LEONARDUS H T"/AU)

L40 102 SEA FILE=HCAPLUS ABB=ON PLU=ON FONG T/AU OR FONG T M/AU OR "FONG TUNG"/AU OR ("FONG TUNG M"/AU OR "FONG TUNG MING"/AU)

L41 90 SEA FILE=HCAPLUS ABB=ON PLU=ON "MACNEIL D"/AU OR "MACNEIL D J"/AU OR ("MACNEIL DOUGLAS"/AU OR "MACNEIL DOUGLAS J"/AU OR "MACNEIL DOUGLAS JOHN"/AU)

L42 1474 SEA FILE=HCAPLUS ABB=ON PLU=ON "CHEN HOWARD"/AU OR ("CHEN HOWARD Y"/AU OR "CHEN HOWARD YONG WEN"/AU) OR CHEN H/AU OR CHEN H Y/AU

L43 81 SEA FILE=HCAPLUS ABB=ON PLU=ON "MARSH DONALD"/AU OR "MARSH DOUGLAS G"/AU OR "MARSH DONALD"/AU OR "MARSH DONALD J"/AU

L44 23 SEA FILE=HCAPLUS ABB=ON PLU=ON ("WARMKE J W"/AU OR "WARMKE JEFFREY"/AU OR "WARMKE JEFFREY W"/AU OR "WARMKE JEFFREY WAYNE"/AU)

L45 14 SEA FILE=HCAPLUS ABB=ON PLU=ON (L38 OR L39 OR L40 OR L41 OR L42 OR L43 OR L44) AND (L11 OR L14 OR L17 OR L20 OR L23)

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L45 ANSWER 1 OF 14 HCAPLUS COPYRIGHT 2006 ACS on STN

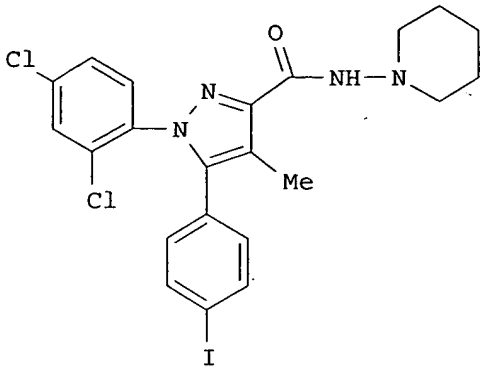
ACCESSION NUMBER: 2006:317218 HCAPLUS
DOCUMENT NUMBER: 144:363116
TITLE: Combination therapy comprising PYY agonists for the treatment of obesity
INVENTOR(S): Amatruda, John M.; Daruwala, Paul; Erondu, Ngozi E.; Macneil, Douglas J.; Moller, David E.; Qian, Su
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 99 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006036770	A2	20060406	WO 2005-US34096	20050922

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2004-612657P P 20040924
OTHER SOURCE(S): MARPAT 144:363116
GI

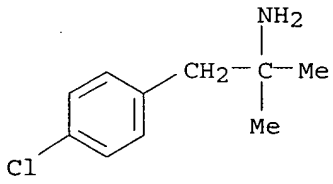


I

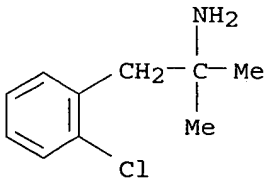
AB The present invention relates to compns. comprising PYY, PYY3-36, or a PYY agonist, and an anti-obesity agent, useful for the treatment and prevention of obesity and obesity-related disorders. The present invention further relates to methods of treating or preventing obesity and obesity-related disorder in a subject in need thereof by administering a composition of the present invention. One example is a in vivo study of the effect of PYY3-36 on 4 h and 16 h food intake and body weight gain in mice and another example is an in vivo study of the effect of the combination of PYY3-36 and CB-1 inverse agonist AM-251 (I) on food intake and body weight in mice.

IT 461-78-9, Chlorphentermine 10389-73-8, Clortermine
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(PPY agonist; combination therapy comprising PYY agonists for the treatment of obesity)

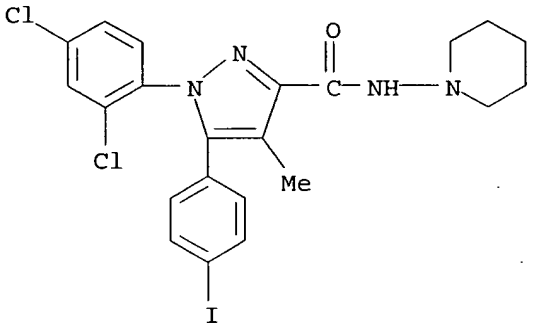
RN 461-78-9 HCAPLUS
CN Benzeneethanamine, 4-chloro-α,α-dimethyl- (9CI) (CA INDEX NAME)



RN 10389-73-8 HCAPLUS
CN Benzeneethanamine, 2-chloro-α,α-dimethyl- (9CI) (CA INDEX NAME)



IT 183232-66-8, AM-251
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination therapy comprising PYY agonists for the treatment of obesity)
RN 183232-66-8 HCAPLUS
CN 1H-Pyrazole-3-carboxamide, 1-(2,4-dichlorophenyl)-5-(4-iodophenyl)-4-methyl-N-1-piperidinyl- (9CI) (CA INDEX NAME)

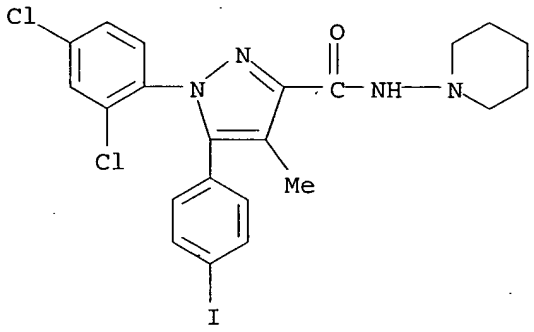


L45 ANSWER 2 OF 14 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:133085 HCAPLUS
DOCUMENT NUMBER: 144:343048
TITLE: F200A substitution in the third transmembrane helix of human cannabinoid CB1 receptor converts AM2233 from receptor agonist to inverse agonist
AUTHOR(S): Shen, Chun-Pyn; Xiao, Jing Chen; Armstrong, Helen; Hagmann, William; Fong, Tung M.
CORPORATE SOURCE: Department of Metabolic Disorders, Merck Research Laboratories, Rahway, NJ, 07065, USA
SOURCE: European Journal of Pharmacology (2006), 531(1-3), 41-46
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB To investigate how specific amino acid residues affect human cannabinoid CB1 receptor binding and activation, CHO cell lines stably expressing wild type and the phenylalanine 200 to alanine mutant of human cannabinoid CB1 receptor (F200A) were examined AM2233 functions as an agonist at the wild type receptor (EC50 = 0.93 nM), but behaves as an inverse agonist at F200A (EC50 = 4.8 nM). The F200A mutant has significantly lower forskolin-stimulated basal cAMP accumulation than that of the wild type, indicating that the F200A mutant possesses higher constitutive activity. F200 does not contribute substantially to the high affinity binding of AM2233 at human cannabinoid CB1 receptor. CP55940, HU-210 and Win55212-2 still function as agonists at the F200A mutant, with similar efficacy, potency, and apparent binding affinity for both wild type human cannabinoid CB1 receptor and F200A mutant. These data indicate that the phenylalanine 200 residue in human cannabinoid CB1 receptor is involved in the receptor activation induced by a specific class of agonists, and supports a model of agonist-structure-dependent conformational changes.
IT 183232-66-8, AM251
RL: PAC (Pharmacological activity); BIOL (Biological study)
(F200A substitution in third transmembrane helix of human cannabinoid

CB1 receptor converts AM2233 from receptor agonist to inverse agonist)

RN 183232-66-8 HCAPLUS

CN 1H-Pyrazole-3-carboxamide, 1-(2,4-dichlorophenyl)-5-(4-iodophenyl)-4-methyl-N-1-piperidinyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L45 ANSWER 3 OF 14 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:1104401 HCAPLUS

DOCUMENT NUMBER: 144:232195

TITLE: Diet induction of monocyte chemoattractant protein-1 and its impact on obesity

AUTHOR(S): Chen, Airu; Mumick, Sheena; Zhang, Chunsheng; Lamb, John; Dai, Hongyue; Weingarth, Drew; Mudgett, John; Chen, Howard; MacNeil, Douglas J.; Reitman, Marc L.; Qian, Su

CORPORATE SOURCE: Department of Metabolic Disorders, Merck Research Laboratories, Rahway, NJ, USA

SOURCE: Obesity Research (2005), 13(8), 1311-1320
CODEN: OBREFR; ISSN: 1071-7323

PUBLISHER: North American Association for the Study of Obesity

DOCUMENT TYPE: Journal

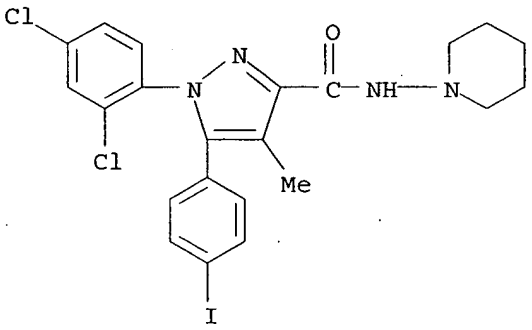
LANGUAGE: English

AB Objective: To examine the effect of a high-fat diet on gene expression in adipose tissues and to determine induction kinetics of adipose monocyte chemoattractant protein-1 and -3 (MCP-1 and MCP-3) in diet-induced obesity (DIO) and the effect of a lack of MCP-1 signaling on DIO susceptibility and macrophage recruitment into adipose tissue. Research Methods and Procedures: Obese and lean adipose tissues were profiled for expression changes. The time-course of MCP-1 and MCP-3 expression was examined by reverse transcriptase-polymerase chain reaction. Plasma MCP-1 levels were determined by ELISA. Chemokine receptor-2 (CCR2) knockout mice were placed on the high-fat diet to determine DIO susceptibility. Macrophage infiltration in adipose tissue was examined by immunohistochem. with F4/80 antibody. Results: DIO elevated adipose expression of many inflammatory genes, including MCP-1 and MCP-3. Adipose MCP-1 and MCP-3 mRNA levels increased within 7 days of starting a high-fat diet, with elevation of plasma MCP-1 detected after 4 wk on the diet. The induction of MCP-1 and MCP-3 expression preceded that of tumor necrosis factor-α. The elevated plasma MCP-1 concentration in obese mice was partially reversed by treatment with AM251. No change in DIO susceptibility and macrophage accumulation in adipose tissue were observed in CCR2 knockout mice, which lack the MCP-1 receptor CCR2. Discussion: A high-fat diet elevated

adipose expression of inflammatory genes, including early induction of MCP-1 and MCP-3, supporting the view that obese adipose tissues contribute to systemic inflammation. However, despite increased MCP-1 in obesity, disruption of MCP-1 signaling did not confer resistance to DIO in mice or reduce adipose tissue macrophage infiltration.

IT 183232-66-8, AM 251
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(diet induction of monocyte chemoattractant protein-1 and impact on obesity in mice fed high-fat diet and effect of antiobesity treatment with AM 251)

RN 183232-66-8 HCAPLUS
CN 1H-Pyrazole-3-carboxamide, 1-(2,4-dichlorophenyl)-5-(4-iodophenyl)-4-methyl-N-1-piperidinyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L45 ANSWER 4 OF 14 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:14148 HCAPLUS
DOCUMENT NUMBER: 142:107413
TITLE: Combination therapy for the treatment of dyslipidemia
INVENTOR(S): Erondu, Ngozi E.; Fong, Tung M.; MacNeil, Douglas J.; Van Der Ploeg, Leonardus H. T.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 106 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005000217	A2	20050106	WO 2004-US17120	20040602
WO 2005000217	A3	20050407		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,

EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

EP 1635813 A2 20060322 EP 2004-753858 20040602
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK

US 2006148721 A1 20060706 US 2005-555194 20051101

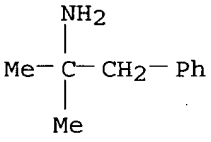
PRIORITY APPLN. INFO.: US 2003-476387P P 20030606
WO 2004-US17120 W 20040602

OTHER SOURCE(S): MARPAT 142:107413

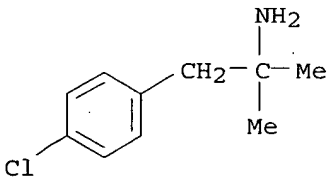
AB The invention relates to compns. comprising an anti-obesity agent and an anti-dyslipidemic agent useful for the treatment of dyslipidemia, dyslipidemia associated with obesity and dyslipidemia-related disorders. The invention further relates to methods of treating or preventing obesity, and obesity-related disorders, in a subject in need thereof by administering a composition of the present invention. The invention further provides pharmaceutical compns., medicaments, and kits useful in carrying out these methods.

IT 122-09-8, Phentermine 461-78-9
10389-73-8, Clortermine
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination therapy for treatment of dyslipidemia)

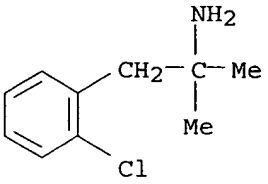
RN 122-09-8 HCAPLUS
CN Benzeneethanamine, α,α-dimethyl- (9CI) (CA INDEX NAME)



RN 461-78-9 HCAPLUS
CN Benzeneethanamine, 4-chloro-α,α-dimethyl- (9CI) (CA INDEX NAME)



RN 10389-73-8 HCAPLUS
CN Benzeneethanamine, 2-chloro-α,α-dimethyl- (9CI) (CA INDEX NAME)



L45 ANSWER 5 OF 14 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:1124587 HCAPLUS
DOCUMENT NUMBER: 142:69188
TITLE: Combination therapy for the treatment of diabetes
INVENTOR(S): Erondu, Ngozi E.; Fong, Tung M.; MacNeil, Douglas J.; Van Der Ploeg, Leonardus H. T.; Kanatani, Akio
PATENT ASSIGNEE(S): Merck & Co., Inc., USA; Banyu Pharmaceutical Co., Ltd.
SOURCE: PCT Int. Appl., 109 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

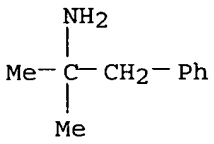
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004110375	A2	20041223	WO 2004-US17291	20040602
WO 2004110375	A3	20050512		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1635832	A2	20060322	EP 2004-753999	20040602
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK				

PRIORITY APPLN. INFO.: US 2003-476388P P 20030606
WO 2004-US17291 W 20040602
OTHER SOURCE(S): MARPAT 142:69188

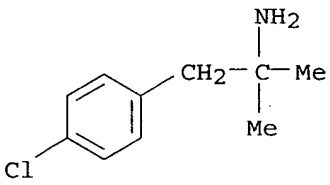
AB The present invention relates to compns. comprising an anti-obesity agent and an anti-diabetic agent useful for the treatment of diabetes, diabetes associated with obesity and diabetes-related disorders. The present invention further relates to methods of treating or preventing obesity, and obesity-related disorders, in a subject in need thereof by administering a composition of the present invention. The present invention further provides for pharmaceutical compns., medicaments, and kits useful in carrying out these methods.

IT 122-09-8, Phentermine 461-78-9, Chlorphentermine 10389-73-8, Clortermine
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination therapy of diabetes and diabetes-related disorders using

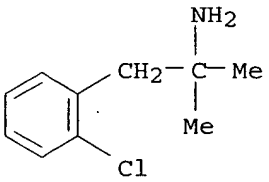
antiobesity agent and antidiabetic agent and other agents)
RN 122-09-8 HCAPLUS
CN Benzeneethanamine, α,α-dimethyl- (9CI) (CA INDEX NAME)



RN 461-78-9 HCAPLUS
CN Benzeneethanamine, 4-chloro-α,α-dimethyl- (9CI) (CA INDEX NAME)



RN 10389-73-8 HCAPLUS
CN Benzeneethanamine, 2-chloro-α,α-dimethyl- (9CI) (CA INDEX NAME)



L45 ANSWER 6 OF 14 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:1124581 HCAPLUS
DOCUMENT NUMBER: 142:69181
TITLE: Combination therapy for the treatment of hypertension
INVENTOR(S): Fong, Tung M.; Erondu, Ngozi E.; Macneil, Douglas J.; Mcintyre, James H.; Van Der Ploeg, Leonardus H. T.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 99 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004110368	A2	20041223	WO 2004-US17090	20040602

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,

CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

EP 1635773 A2 20060322 EP 2004-753832 20040602
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR

US 2006160834 A1 20060720 US 2005-559111 20051202

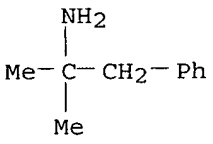
PRIORITY APPLN. INFO.: US 2003-476390P P 20030606
WO 2004-US17090 W 20040602

OTHER SOURCE(S): MARPAT 142:69181

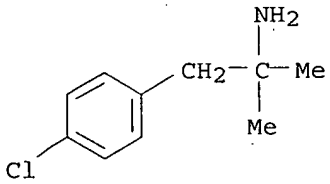
AB The present invention relates to compns. comprising an anti-obesity agent and an anti-hypertensive agent useful for the treatment of hypertension, hypertension associated with obesity, and hypertension-related disorders. The present invention further relates to methods of treating or preventing obesity, and obesity-related disorders, in a subject in need thereof by administering a composition of the present invention. The present invention further provides for pharmaceutical compns., medicaments, and kits useful in carrying out these methods.

IT 122-09-8, Phentermine 461-78-9, Chlorphentermine 10389-73-8, Clortermine
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination therapy of hypertension and hypertension-related disorders using antiobesity agent and antihypertensive agent and other agents and antihypertensive agent)

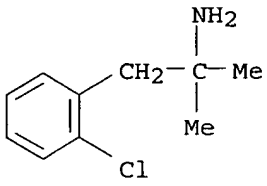
RN 122-09-8 HCAPLUS
CN Benzeneethanamine, α,α-dimethyl- (9CI) (CA INDEX NAME)



RN 461-78-9 HCAPLUS
CN Benzeneethanamine, 4-chloro-α,α-dimethyl- (9CI) (CA INDEX NAME)



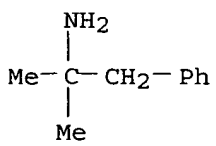
RN 10389-73-8 HCAPLUS
CN Benzeneethanamine, 2-chloro-α,α-dimethyl- (9CI) (CA INDEX NAME)



L45 ANSWER 7 OF 14 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:513332 HCAPLUS
DOCUMENT NUMBER: 141:47361
TITLE: Combination therapy using an appetite suppressant and/or a metabolic rate enhancer and/or a nutrient absorption inhibitor for the treatment of obesity and obesity-related disorders
INVENTOR(S): Nargund, Ravi P.; Van der Ploeg, Leonardus H. T.; Fong, Tung M.; MacNeil, Douglas J.; Chen, Howard Y.; Marsh, Donald J.; Warmke, Jeffrey
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 43 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

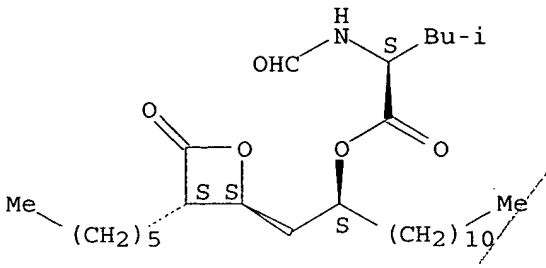
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004122033	A1	20040624	US 2003-730704	20031208
PRIORITY APPLN. INFO.:			US 2002-432063P	P 20021210

AB The invention discloses compns. comprising an appetite suppressant and/or a metabolic rate enhancer and/or a nutrient absorption inhibitor useful for the treatment of obesity, and obesity-related disorders. The invention also discloses methods for treating or preventing obesity and obesity-related disorders in a subject in need thereof by administering a composition of the invention. The invention further discloses pharmaceutical compns., medicaments, and kits useful in carrying out the methods. Preparation of 11β-hydroxysteroid dehydrogenase 1 inhibitors is included.
IT 122-09-8, Phentermine 96829-58-2, Orlistat 183232-66-8, AM 251
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(appetite suppressant and/or metabolic rate enhancer and/or nutrient absorption inhibitor for treatment of obesity and obesity-related disorders)
RN 122-09-8 HCAPLUS
CN Benzeneethanamine, α,α-dimethyl- (9CI) (CA INDEX NAME)

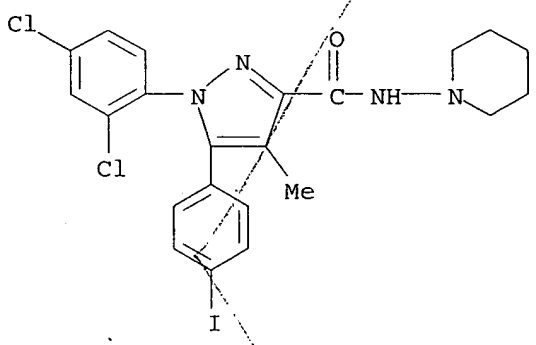


RN 96829-58-2 HCAPLUS
CN L-Leucine, N-formyl-, (1S)-1-[[(2S,3S)-3-hexyl-4-oxo-2-oxetanyl]methyl]dodecyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 183232-66-8 HCAPLUS
CN 1H-Pyrazole-3-carboxamide, 1-(2,4-dichlorophenyl)-5-(4-iodophenyl)-4-methyl-N-1-piperidinyl- (9CI) (CA INDEX NAME)



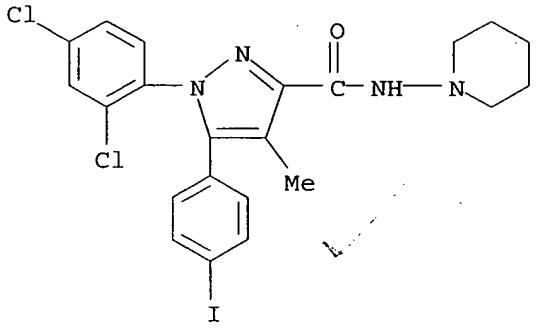
L45 ANSWER 8 OF 14 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:94835 HCAPLUS
DOCUMENT NUMBER: 140:297332
TITLE: Synergistic effects of cannabinoid inverse agonist AM251 and opioid antagonist nalmefene on food intake in mice
AUTHOR(S): Chen, Richard Z.; Huang, Ruey-Ruey C.; Shen, Chun-Pyn; MacNeil, Douglas J.; Fong, Tung M.
CORPORATE SOURCE: Department of Metabolic Disorders, Merck Research Laboratories, Rahway, NJ, 07065, USA
SOURCE: Brain Research (2004), 999(2), 227-230
CODEN: BRREAP; ISSN: 0006-8993
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Oral administration of the opioid antagonist nalmefene alone (up to 20 mg/kg) failed to show a significant effect on acute food intake in mice. However, combined oral dosing of nalmefene and subthreshold doses of AM251, a cannabinoid CB1 receptor inverse agonist, led to a significant reduction in food intake in both lean and diet-induced obese (DIO) mice. Furthermore, the anorectic effect of a high dose of AM251 was further enhanced when co-administered with nalmefene. The results

support a synergistic interaction between opioid and cannabinoid systems in regulating feeding behavior.

IT 183232-66-8, AM251
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(synergistic effects of AM251 and nalmefene on food intake in mice)

RN 183232-66-8 HCAPLUS

CN 1H-Pyrazole-3-carboxamide, 1-(2,4-dichlorophenyl)-5-(4-iodophenyl)-4-methyl-N-1-piperidinyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L45 ANSWER 9 OF 14 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2004:80448 HCAPLUS

DOCUMENT NUMBER: 140:122817

TITLE: NPY5 antagonist-antiobesity agent combination for the prevention and treatment of diabetes, obesity, and obesity-related disorders

INVENTOR(S): Macneil, Douglas J.; Mcintyre, James H.; Van Der Ploeg, Leonardus H. T.; Ishihara, Akane

PATENT ASSIGNEE(S): Merck & Co., Inc., USA; Banyu Pharmaceutical Co., Ltd.

SOURCE: PCT Int. Appl., 134 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004009015	A2	20040129	WO 2003-US22077	20030714
WO 2004009015	A3	20040304		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2492225	AA	20040129	CA 2003-2492225	20030714
AU 2003253925	A1	20040209	AU 2003-253925	20030714
EP 1534074	A2	20050601	EP 2003-765587	20030714
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
JP 2005533849	T2	20051110	JP 2004-523149	20030714
US 2005288213	A1	20051229	US 2005-520566	20050107
PRIORITY APPLN. INFO.:			US 2002-396603P	P 20020718
			US 2002-417999P	P 20021011
			WO 2003-US22077	W 20030714

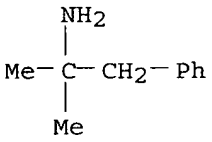
OTHER SOURCE(S): MARPAT 140:122817

AB The invention discloses compns. comprising a NPY5 antagonist and an antiobesity agent, useful for the treatment and prevention of diabetes, obesity, and obesity-related disorders. The invention also discloses methods of treating or preventing obesity and obesity-related disorders in a subject in need thereof by administering a composition of the invention. The invention further discloses pharmaceutical compns., medicaments, and kits useful in carrying out the methods.

IT 122-09-8, Phentermine 461-78-9, Chlorphentermine 10389-73-8, Clortermine 96829-58-2, Orlistat
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(NPY5 antagonist-antiobesity agent combination for the prevention and treatment of diabetes, obesity, and obesity-related disorders)

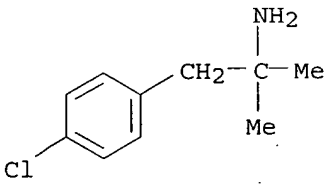
RN 122-09-8 HCAPLUS

CN Benzeneethanamine, α,α-dimethyl- (9CI) (CA INDEX NAME)



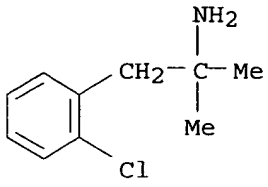
RN 461-78-9 HCAPLUS

CN Benzeneethanamine, 4-chloro-α,α-dimethyl- (9CI) (CA INDEX NAME)



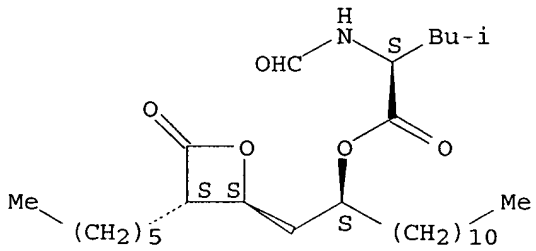
RN 10389-73-8 HCAPLUS

CN Benzeneethanamine, 2-chloro-α,α-dimethyl- (9CI) (CA INDEX NAME)



RN 96829-58-2 HCAPLUS
CN L-Leucine, N-formyl-, (1S)-1-[[(2S,3S)-3-hexyl-4-oxo-2-oxetanyl]methyl]dodecyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L45 ANSWER 10 OF 14 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:737505 HCAPLUS
DOCUMENT NUMBER: 139:255308
TITLE: Agouti-related protein as biomarker for efficacy of appetite suppressant drugs
INVENTOR(S): Fong, Tung M.; Shen, Chun-Pyn; Van der Ploeg, Leonardus H. T.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 36 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2003075742	A2	20030918	WO 2003-US6437		20030303
WO 2003075742	A3	20040401			
W: CA, JP, US					
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR					
CA 2477614	AA	20030918	CA 2003-2477614		20030303
EP 1483580	A2	20041208	EP 2003-711370		20030303
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, SK					
US 2005169839	A1	20050804	US 2003-506577		20030303
PRIORITY APPLN. INFO.:			US 2002-361806P	P	20020305
			WO 2003-US6437	W	20030303

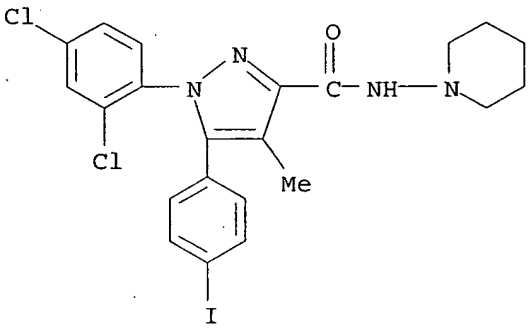
AB The present invention relates to agouti-related protein (AGRP) as a biomarker for the efficacy of appetite suppressant drugs given to humans or other mammals for the treatment of obesity. It further relates to a

novel method of determining the efficacy of a test compound given to a subject for the treatment of obesity, wherein the test compound is an appetite suppressant which does not stimulate the release of serotonin. It also relates to a method for following the progress of a therapeutic regime designed to alleviate obesity and to a method for determining the appropriate dosage of an appetite suppressant given to a subject for the treatment of obesity. Plasma levels of AGRP in lean rats were measured by RIA after treatment with various appetite suppressants. AGRP plasma levels were reduced by AM251, a cannabinoid CB1 inverse agonist, and by sibutramine.

IT 183232-66-8, AM 251
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(CB1R inverse agonist, plasma AGRP levels in lean rats after treatment with; agouti-related protein as biomarker for efficacy of appetite suppressant drugs)

RN 183232-66-8 HCAPLUS

CN 1H-Pyrazole-3-carboxamide, 1-(2,4-dichlorophenyl)-5-(4-iodophenyl)-4-methyl-N-1-piperidinyl- (9CI) (CA INDEX NAME)



L45 ANSWER 11 OF 14 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2001:806135 HCAPLUS

DOCUMENT NUMBER: 137:52225

TITLE: Preparation of double-encapsulated microcapsules for mitigating drug loss and extending release

AUTHOR(S): Tsai, Y.-L.; Jong, C.-C.; Chen, H.

CORPORATE SOURCE: Department of Chemical Engineering, National Central University, Chung-Li, 320, Taiwan

SOURCE: Journal of Microencapsulation (2001), 18(6), 701-711
CODEN: JOMIEF; ISSN: 0265-2048

PUBLISHER: Taylor & Francis Ltd.

DOCUMENT TYPE: Journal

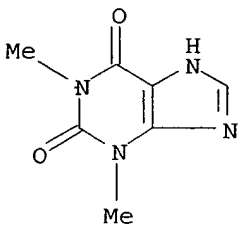
LANGUAGE: English

AB The double-encapsulated microcapsules were prepared by the non-solvent addition, phase-separation method to form core material and, encapsulated with the O/W emulsion non-solvent addition method to increase drug loading and regulate drug release rate. The drug used was theophylline, which is water-soluble Dichloromethane and n-hexane were used as the solvent and non-solvent, resp. This study investigated how various core material and microcapsule Et cellulose/theophylline ratios affect the drug loss, particle size, surface morphol. and release rate. The drug loss of the double-encapsulated microcapsules was 12.8% less than that of

microcapsules prepared by the O/W emulsion non-solvent addition method alone. The particle size of these double-encapsulated microcapsules decreased as the concentration of EC polymer was increased in the second encapsulation process. The roughness of their surface was also in proportion to the concentration of polymer solution used in the second encapsulation process. The dissoln. study showed that the T20 of the double-encapsulated microcapsules ranged from 2-35.4 h, while that of the O/W emulsion non-solvent addition method microcapsules was from 2.7-7.7 h. The greater the level of EC in the polymer solution, the slower the release rate of the drug from the microcapsules when the EC was not over the critical amount

IT 58-55-9, Theophylline, biological studies
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(double-encapsulated microcapsules for mitigating drug loss and extending release)

RN 58-55-9 HCAPLUS
CN 1H-Purine-2,6-dione, 3,7-dihydro-1,3-dimethyl- (9CI) (CA INDEX NAME)

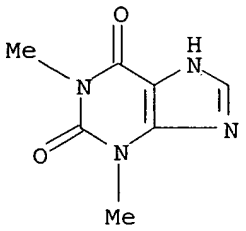


REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L45 ANSWER 12 OF 14 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:477986 HCAPLUS
DOCUMENT NUMBER: 133:182875
TITLE: The preparation and drug-release behavior of CTA/EC and PMS/EC composite microcapsules
AUTHOR(S): Tsai, Y.-L.; Tien, H.-T.; Chen, H.
CORPORATE SOURCE: Department of Chemical Engineering, National Central University, Chung-Li, 320, Taiwan
SOURCE: Journal of Microencapsulation (2000), 17(4), 413-424
CODEN: JOMIEF; ISSN: 0265-2048
PUBLISHER: Taylor & Francis Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A cellulose triacetate (CTA) and 3 different mol. wts. of poly(α-methyltyrene) (PMS) were used as co-wall materials to prepare composite microcapsules with Et cellulose (EC). A non-solvent-addition phase-separation method was used. The core material was theophylline (TH) and the solvent-non-solvent pair was dichloromethane-n-hexane, and the drug-release rates of the microcapsules prepared from these 2 types of co-wall materials were compared. The effects of their phase-separation range on the properties of the microcapsules, such as particle size, release rate and the morphol. of the microcapsules are also discussed. The release rate of microcapsules was also affected by the compatibility of the co-wall materials and the EC. The dissoln. studies indicated that the drug-release time of CTA/EC and PMS/EC composite microcapsules was sustained to 10- and 3.5-fold, resp., in comparison with that for pure EC microcapsules.

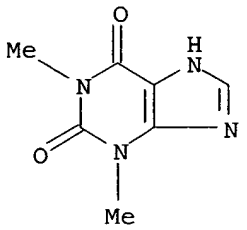
IT 58-55-9, Theophylline, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation and drug-release behavior of cellulose/polymethylstyrene composite microcapsules)
RN 58-55-9 HCAPLUS
CN 1H-Purine-2,6-dione, 3,7-dihydro-1,3-dimethyl- (9CI) (CA INDEX NAME)



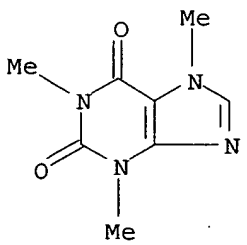
REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L45 ANSWER 13 OF 14 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1994:491606 HCAPLUS
DOCUMENT NUMBER: 121:91606
TITLE: Effect of the solvent-non-solvent pairs on the surface morphology and release behavior of ethyl cellulose microcapsules prepared by non-solvent-addition phase separation method
AUTHOR(S): Wu, J. C.; Su, S. G.; Shyu, S. S.; Chen, H.
CORPORATE SOURCE: Dep. Chem. Eng., Natl. Cent. Univ., Chungli, 320, Taiwan
SOURCE: Journal of Microencapsulation (1994), 11(3), 297-308
CODEN: JOMIEF; ISSN: 0265-2048
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Four solvent-non-solvent pairs (Et acetate-cyclohexane, dichloromethane-cyclohexane, acetone-cyclohexane and dichloromethane-n-hexane) with different solubility parameter differences were chosen to prepare Et cellulose microcapsules containing theophylline by using non-solvent-addition phase separation method. The results showed that the surface morphol. and release behavior of microcapsules were greatly affected by different solvent-non-solvent pairs. The surface of the microcapsules prepared from the system of high solubility parameter difference was more smooth than those from the systems of low solubility parameter difference. The release rate of the drug from microcapsules decreased with increasing solubility parameter difference of the preparative system. The determination of the wall thickness and porosity of the microcapsules could reasonably explain the release characteristics. The porosity of the microcapsules decreased with the increase of solubility parameter difference of the preparative system, but the wall thickness of the microcapsules showed a corresponding increase. The release of the drug from various ethylcellulose microcapsules fitted first-order kinetics with biphasic release profiles.
IT 58-55-9, Theophylline, biological studies
RL: BIOL (Biological study)
(Et cellulose microcapsules containing, solvent-nonsolvent pairs effect on drug release and surface morphol. of)

RN 58-55-9 HCAPLUS
CN 1H-Purine-2,6-dione, 3,7-dihydro-1,3-dimethyl- (9CI) (CA INDEX NAME)



L45 ANSWER 14 OF 14 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1989:219007 HCAPLUS
DOCUMENT NUMBER: 110:219007
TITLE: The effect of the addition of low-molecular weight poly(DL-lactide) on drug release from biodegradable poly(DL-lactide) drug delivery systems
AUTHOR(S): Bodmeier, R.; Oh, K. H.; Chen, H.
CORPORATE SOURCE: Coll. Pharm., Univ. Texas, Austin, TX, 78712-1074, USA
SOURCE: International Journal of Pharmaceutics (1989), 51(1), 1-8
CODEN: IJPHDE; ISSN: 0378-5173
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Biodegradable films and microspheres were prepared from blends of high- and low-mol. weight poly(DL-lactide) (I) with mol. wts. of 120,000 and 2000, resp., by solvent casting and an emulsification-solvent evaporation method. Salicylic acid, caffeine, and quinidine were chosen as model compds. DSC and SEM were used to characterize the films and microspheres. The addition of low-mol. weight I clearly accelerated the release of drug from both films and microspheres. Biodegradable drug delivery systems were prepared with durations of action between several hours to months by varying the amount of low-mol. weight I. This technique allowed control over the drug release with a single, biodegradable homopolymer. In the case of quinidine, interactions with the carboxyl groups of I occurred and complicated the release pattern.
IT 58-08-2, Caffeine, biological studies
RL: BIOL (Biological study)
(release of, from biodegradable polylactide delivery systems, low-mol. weight polymer effect on)
RN 58-08-2 HCAPLUS
CN 1H-Purine-2,6-dione, 3,7-dihydro-1,3,7-trimethyl- (9CI) (CA INDEX NAME)



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L4            48 SEA FILE=REGISTRY ABB=ON  PLU=ON  PHENTERMINE NOT L3
L5             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  THEOPHYLLINE/CN
L6          2785 SEA FILE=REGISTRY ABB=ON  PLU=ON  THEOPHYLLINE
L7          2784 SEA FILE=REGISTRY ABB=ON  PLU=ON  L6 NOT L5
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L10          127 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L9
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L13         1053 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L12
L14         1862 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L13 OR L4 OR ?PHENTERMINE?
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L23        48194 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L22 OR L7 OR ?THEOPHYLLIN?
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L25            0 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L11 AND L17
L26            2 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L11 AND L20
L27            0 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L17 AND (L23 OR L20)
L28            4 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L24 OR L25 OR L26 OR L27
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                 L42 OR L43 OR L44)
L48           41 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L39 AND (L40 OR L41 OR L42 OR
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L53  ANSWER 1 OF 62  HCAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:        2006:600146  HCAPLUS
TITLE:                   Melanocortin-4 receptor (MC4R) agonists for the
                         treatment of obesity
AUTHOR(S):               Nargund, Ravi P.; Strack, Alison M.;
                         Fong, Tung M.
CORPORATE SOURCE:        Merck Research Laboratories, Rahway, NJ, 07065, USA
SOURCE:                  Journal of Medicinal Chemistry (2006), 49(14),
                         4035-4043
                         CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER:               American Chemical Society
DOCUMENT TYPE:           Journal; General Review
LANGUAGE:                English
AB   The role of melanocortin-4 receptor (MC4R) as an antiobesity target is
     considered.  Pharmacol. of melanocortin peptides and design considerations
     for MC4R agonists are discussed, with emphasis on some recent developments
     in the design of privileged structure-based and non-peptide MC4R agonists.
     The structure-function relationship and neurophysiol. of MC4R are also
     covered, along with the role of melanocortins in sexual function.
REFERENCE COUNT:         100   THERE ARE 100 CITED REFERENCES AVAILABLE FOR
                               THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE
                               FORMAT

L53  ANSWER 2 OF 62  HCAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:        2005:1341986  HCAPLUS
DOCUMENT NUMBER:         144:232941
TITLE:                   Synthesis of functionalized 1,8-naphthyridinones and
                         their evaluation as novel, orally active CB1 receptor
                         inverse agonists
AUTHOR(S):               Debenham, John S.; Madsen-Duggan, Christina B.; Walsh,
                         Thomas F.; Wang, Junying; Tong, Xinchun; Doss, George
                         A.; Lao, Julie; Fong, Tung M.; Schaeffer,
                         Marie-Therese; Xiao, Jing Chen; Huang, Cathy R.-R. C.;
                         Shen, Chun-Pyn; Feng, Yue; Marsh, Donald J.;
                         Stribling, D. Sloan; Shearman, Lauren P.; Strack,
                         Alison M.; MacIntyre, D. Euan; Van der Ploeg, Lex H.
                         T.; Goulet, Mark T.
CORPORATE SOURCE:        Department of Medicinal Chemistry, Merck Research
                         Laboratories, Rahway, NJ, 07065, USA
SOURCE:                  Bioorganic & Medicinal Chemistry Letters (2006),
                         16(3), 681-685
                         CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER:               Elsevier B.V.
DOCUMENT TYPE:           Journal
LANGUAGE:                English
OTHER SOURCE(S):         CASREACT 144:232941
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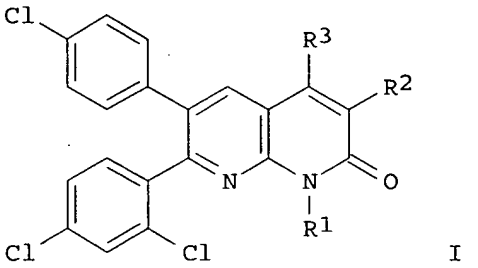


I

AB Synthesis, SAR, and binding affinities are described for a new class of 1,8-naphthyridinones I (R1 = H, Me, Me2CHCH2, MeOCH2CH2, PhCH2, etc.; R2 = H, Me, CN, MeO, Me2N, Me2CH, MeCO; R3 = Me, H2N, Me2N, MeCONH, HOCH2CONH, etc.) as CB1 receptor specific inverse agonists. Food intake, knockout mouse, and pharmacokinetic evaluation of I (R1 = Me; R2 = MeCO; R3 = MeCONH) indicate that this compound is an effective orally active modulator of CB1.

REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L53 ANSWER 3 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:739598 HCAPLUS
TITLE: SAR and pharmocology of potent and selective melanocortin subtype-4 receptor agonists with azabicyclo carboxamide moiety
AUTHOR(S): Guo, Liangqin; Ye, Zhixiong; Barakat, Khaled J.; Pollard, Patrick G.; Palucki, Brenda L.; Sebhat, Iyassu K.; Bakshi, Raman K.; Tang, Rui; Kalyani, Rubana N.; Vongs, Aurawan; Rosenblum, Charles I.; MacNeil, Tanya; Weinberg, David H.; Peng, Qianping; Tamvakopoulos, Constantin; Miller, Randy R.; Stearns, Ralph A.; McGowan, Erin; Martin, William J.; Chen, Airu S.; Metzger, Joseph M.; Chen, Howard Y. ; Strack, Alison M.; MacIntyre, Euan; Van der Ploeg, Lex H. T.; Wyvratt, Matthew J.; Nargund, Ravi P.
CORPORATE SOURCE: Medicinal Chemistry, Merck Research Laboratories, Rahway, NJ, 07065, USA
SOURCE: Abstracts of Papers, 230th ACS National Meeting, Washington, DC, United States, Aug. 28-Sept. 1, 2005 (2005), MEDI-083. American Chemical Society: Washington, D. C.
CODEN: 69HFCL
DOCUMENT TYPE: Conference; Meeting Abstract; (computer optical disk)
LANGUAGE: English

AB The melanocortin receptors are part of the family of five seven-transmembrane G-protein-coupled receptors and mediate a variety of physiol. functions. The melanocortin subtype-4 receptor (MC4R) has been linked to the regulation of energy homeostasis, feeding regulation and sexual functions. Considerable research effort has been spent on identifying selective non-peptide MC4R agonists for potential treatment for obesity and sexual dysfunction. In this presentation we report the discovery of a series of isoquinuclidines containing MC4R agonists which

possess potent in vitro and in vivo activities towards MC4R and show attenuated undesirable ancillary activities such as bioactivation leading to covalent binding to proteins. Compound 1 was the most interesting analog identified in this series and was studied in considerable detail. It exhibits excellent binding affinity (IC50 = 8 nM) and functional activity (EC50 = 11 nM with 81% activation). Furthermore, it is efficacious in lowering food intake in both rats and mice at 20 mpk PO. The synthesis, structure-activity-relationship studies and pharmacol. of selected compds. in this series will be discussed.

L53 ANSWER 4 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:589330 HCAPLUS

DOCUMENT NUMBER: 143:259480

TITLE: Discovery and activity of (1R,4S,6R)-N-[(1R)-2-[4-cyclohexyl-4-[[(1,1-dimethylethyl)amino]carbonyl]-1-piperidinyl]-1-[(4-fluorophenyl)methyl]-2-oxoethyl]-2-methyl-2-azabicyclo[2.2.2]octane-6-carboxamide (3, RY764), a potent and selective melanocortin subtype-4 receptor agonist

AUTHOR(S): Ye, Zhixiong; Guo, Lianggin; Barakat, Khaled J.; Pollard, Patrick G.; Palucki, Brenda L.; Sebhat, Iyassu K.; Bakshi, Raman K.; Tang, Rui; Kalyani, Rubana N.; Vongs, Aurawan; Chen, Airu S.; Chen, Howard Y.; Rosenblum, Charles I.; MacNeil, Tanya; Weinberg, David H.; Peng, Qianping; Tamvakopoulos, Constantin; Miller, Randy R.; Stearns, Ralph A.; Cashen, Doreen E.; Martin, William J.; Metzger, Joseph M.; Strack, Alison M.; MacIntyre, D. Euan; Van der Ploeg, Lex H. T.; Patchett, Arthur A.; Wyvratt, Matthew J.; Nargund, Ravi P.

CORPORATE SOURCE: Department of Medicinal Chemistry, Merck Research Laboratories, Rahway, NJ, 07065-0900, USA

SOURCE: Bioorganic & Medicinal Chemistry Letters (2005), 15(15), 3501-3505
CODEN: BMCLE8; ISSN: 0960-894X

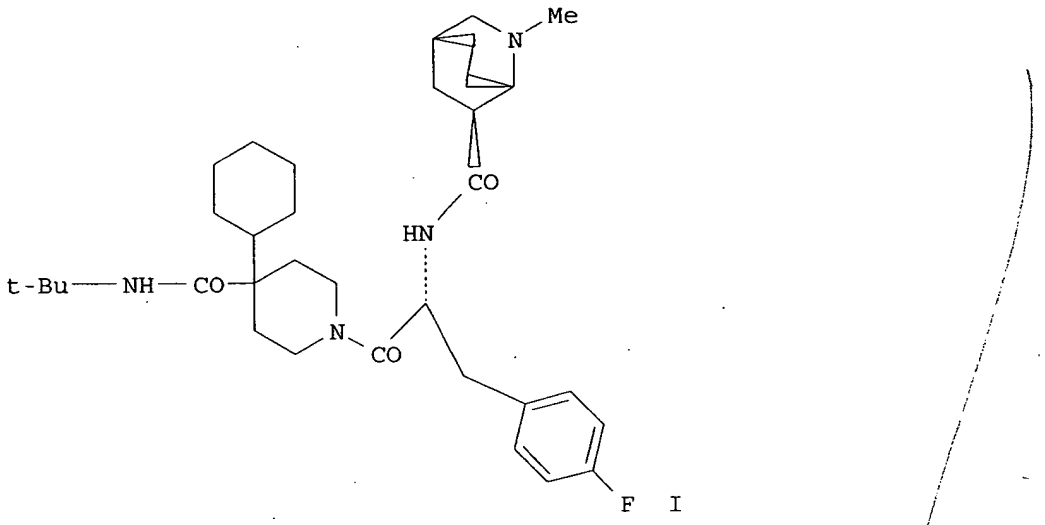
PUBLISHER: Elsevier B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 143:259480

GI



AB A novel isoquinuclidine containing selective melanocortin subtype-4 receptor small mol. agonist (I), (RY764), is reported. Its in vivo characterization revealed mechanism-based food intake reduction and erectile activity augmentation in rodents.

REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L53 ANSWER 5 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:575239 HCAPLUS
DOCUMENT NUMBER: 143:126453
TITLE: Antiobesity effect of a melanin-concentrating hormone 1 receptor antagonist in diet-induced obese mice
AUTHOR(S): Mashiko, Satoshi; Ishihara, Akane; Gomori, Akira; Moriya, Ryuichi; Ito, Makoto; Iwaasa, Hisashi; Matsuda, Masao; Feng, Yue; Shen, Zhu; Marsh, Donald J.; Bednarek, Maria A.; MacNeil, Douglas J.; Kanatani, Akio
CORPORATE SOURCE: Tsukuba Research Institute, Banyu Pharmaceutical Co., Ltd., Tsukuba, 300-2611, Japan
SOURCE: Endocrinology (2005), 146(7), 3080-3086
CODEN: ENDOAO; ISSN: 0013-7227
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Melanin-concentrating hormone (MCH) is a cyclic orexigenic peptide expressed in the lateral hypothalamus, which plays an important role in regulating energy balance. To elucidate the physiol. role of MCH in obesity development, the present study examined the effect of a selective MCH1 receptor (MCH1R) antagonist in the diet-induced obesity mouse model. The MCH1R antagonist has high affinity and selectivity for MCH-1R and potently inhibits intracerebroventricularly injected MCH-induced food intake in Sprague Dawley rats. Chronic intracerebroventricular infusion of the MCH1R antagonist (7.5 μg/d) completely suppressed body weight gain in diet-induced obese mice during the treatment periods and significantly decreased cumulative food intake, by 14%. Carcass anal. showed that the MCH1R antagonist resulted in a selective decrease of body fat in the diet-induced obese mice. In addition, the MCH1R antagonist ameliorated the obesity-related hypercholesterolemia, hyperinsulinemia, hyperglycemia, and

hyperleptinemia. These results indicate that MCH has a major role in the development of diet-induced obesity in mice and that a MCH1R antagonist might be a useful candidate as an antiobesity agent.

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L53 ANSWER 6 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:543877 HCAPLUS
DOCUMENT NUMBER: 143:280886
TITLE: Effects of Melanocortin Receptor Activation and Blockade on Ethanol Intake: A Possible Role for the Melanocortin-4 Receptor
AUTHOR(S): Navarro, Montserrat; Cubero, Inmaculada; Chen, Airu S.; Chen, Howard Y.; Knapp, Darin J.; Breese, George R.; Marsh, Donald J.; Thiele, Todd E.
CORPORATE SOURCE: Department of Psychology, Bowles Center for Alcohol Studies, University of North Carolina, Chapel Hill, NC, USA
SOURCE: Alcoholism: Clinical and Experimental Research (2005), 29(6), 949-957
CODEN: ACRSDM; ISSN: 0145-6008
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Background: The melanocortin (MC) system is composed of peptides that are cleaved from the polypeptide precursor pro-opiomelanocortin. A growing body of literature suggests that the MC system modulates neurobiol. responses to drugs of abuse. Because ethanol has direct effects on central pro-opiomelanocortin activity, it is possible that MC neuropeptides participate in the control of voluntary ethanol consumption. Here we assessed the possibility that MC receptor (MCR) agonists modulate ethanol intake via the MC3 receptor (MC3R) and/or the MC4 receptor (MC4R) and whether the MCR antagonist AgRP-(83-132) controls ethanol consumption. Methods: Mc3r-deficient (Mc3r\-/-) and wild-type (Mc3r+/+) littermate mice were given i.p. (10 mg/kg) and intracerebroventricular (1.0 μg ICV) doses of melanotan II (MTII), a nonselective MCR agonist. To assess the role of MC4R, C57BL/6J mice were given an ICV infusion of the highly selective MC4R agonist cyclo(NH-CH2-CH2-CO-His-D-Phe-Arg-Trp-Glu)-NH2 (1.0 or 3.0 μg). Finally, naive C57BL/6J mice were given an ICV infusion of AgRP-(83-132) (0.05 and 1.0 μg). Results: MTII was similarly effective at reducing ethanol drinking in Mc3r-deficient (Mc3r-/-) and wild-type (Mc3r+/+) littermate mice. Furthermore, ICV infusion of the MC4R agonist significantly reduced ethanol drinking, whereas ICV infusion of AgRP-(83-132) significantly increased ethanol drinking in C57BL/6J mice. Neither MTII nor AgRP-(83-132) altered blood ethanol levels at doses that modulated ethanol drinking. Conclusions: The present results suggest that MC4R, and not MC3R, modulates MCR agonist-induced reduction of ethanol consumption and that ethanol intake is increased by the antagonistic actions of AgRP-(83-132). These findings strengthen the argument that MCR signaling controls ethanol consumption and that compds. directed at MCR may represent promising targets for treating alc. abuse disorders in addition to obesity.

REFERENCE COUNT: 78 THERE ARE 78 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L53 ANSWER 7 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:519935 HCAPLUS
DOCUMENT NUMBER: 141:64952
TITLE: Chronic administration of nalmefene leads to increased

food intake and body weight gain in mice
AUTHOR(S): Chen, Richard Z.; Huang, Ruey-Ruey C.; Shen, Chun-Pyn; MacNeil, Douglas J.; Fong, Tung M.
CORPORATE SOURCE: Department of Metabolic Disorders, Merck Research Laboratories, Rahway, NJ, 07065, USA
SOURCE: European Journal of Pharmacology (2004), 495(1), 63-66
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Nalmefene is an orally available opioid receptor antagonist that has been shown to suppress appetite in humans, but its effects on chronic food intake and body weight remain unclear. Here, we report that chronic (21-day) oral administration of nalmefene at 2 or 10 mg/kg/day in diet-induced obese (DIO) mice led to significant increases (9-11%) in cumulative food intake. Mice in the nalmefene-treated groups also gained body weight at a rate faster than the control. Body composition anal. showed that the extra body weight gains in the treated animals were mostly due to increased fat accumulation. Since acute nalmefene treatment showed a trend toward a decrease rather than an increase in food intake, it is possible that the orexigenic effect of chronic oral administration of nalmefene was caused by pharmacol. active metabolites rather than the drug itself. Our results argue against the potential use of nalmefene for treating human obesity.

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L53 ANSWER 8 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:485530 HCAPLUS
DOCUMENT NUMBER: 141:34656
TITLE: Agouti-related protein deficient cells and non-human transgenic animals, and methods of selecting compounds which regulate energy metabolism
INVENTOR(S): Qian, Su; Van Der Ploeg, Leonardus H. T.; Chen, Howard Y.; Weingarth, Drew T.; Trumbauer, Myrna E.; Metzger, Joseph M.
PATENT ASSIGNEE(S): Merck and Co., Inc., USA
SOURCE: PCT Int. Appl., 64 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2004004447	A2	20040115	WO 2003-US20245		20030627
W: CA, JP, US					
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR					
JP 2006506968	T2	20060302	JP 2004-519657		20030627
US 2005257279	A1	20051117	US 2004-518955		20041217
PRIORITY APPLN. INFO.:			US 2002-393391P	P	20020703
			WO 2003-US20245	W	20030627

AB Cells and non-human transgenic animals have been engineered to be deficient in the gene encoding agouti-related protein (AgRP), a neuropeptide expressed in the hypothalamus and known to potently stimulate feeding and body weight gain in rodents. AgRP-deficient transgenic animals have a reduced day time RQ, indicating that AgRP is involved in the regulation of energy metabolism, resulting in the reduced usage of fat as an energy source. Agrp-/- mice are viable, and exhibit normal locomotor

activity, growth rates, and food intake. These AgRP-deficient transgenic animals can be used to select for and test potential modulators of AgRP. This data allows for methods of screening for AgRP modulators which regulate energy metabolism and caloric utilization. The disclosure also relates to a neuropeptide Y (NPY)/AgRP double-knockout mouse which can be used to select for and test potential modulators (e.g., agonists or antagonists) of AgRP and/or NPY. Combined data on ghrelin and a known ghrelin peptidomimetic compound indicate that removal of NPY severely compromises the feeding promotion of ghrelin, while the loss of AgRP does not by itself diminish the signaling of circulating ghrelin. Single- and double-knockout mice demonstrate that one of the in vivo functions of NPY and AgRP is to relay peripheral ghrelin signaling.

L53 ANSWER 9 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:429357 HCAPLUS
DOCUMENT NUMBER: 141:17934
TITLE: Orexigenic action of peripheral ghrelin is mediated by neuropeptide Y and agouti-related protein
AUTHOR(S): Chen, H. Y.; Trumbauer, M. E.; Chen, A. S.; Weingarth, D. T.; Adams, J. R.; Frazier, E. G.; Shen, Z.; Marsh, D. J.; Feighner, S. D.; Guan, X.-M.; Ye, Z.; Nargund, R. P.; Smith, R. G.; Van Der Ploeg, L. H. T.; Howard, A. D.; Macneil, D. J.; Qian, S.
CORPORATE SOURCE: Department of Metabolic Disorders, Merck Research Laboratories, Rahway, NJ, 07065, USA
SOURCE: Endocrinology (2004), 145(6), 2607-2612
CODEN: ENDOAO; ISSN: 0013-7227
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Ghrelin, a stomach-derived orexigenic hormone, has stimulated great interest as a potential target for obesity control. Pharmacol. evidence indicates that ghrelin's effects on food intake are mediated by neuropeptide Y (NPY) and agouti-related protein (AgRP) in the central nervous system. These include intracerebroventricular application of antibodies to neutralize NPY and AgRP, and the application of an NPY Y1 receptor antagonist, which blocks some of the orexigenic effects of ghrelin. Here the authors describe treatment of Agrp-/-;Npy-/- and Mc3r-/-;Mc4r-/- double knockout mice as well as Npy-/- and Agrp-/- single knockout mice with either ghrelin or an orally active nonpeptide ghrelin agonist. The data demonstrate that NPY and AgRP are required for the orexigenic effects of ghrelin, as well as the involvement of the melanocortin pathway in ghrelin signaling. The authors' results outline a functional interaction between the NPY and AgRP pathways. Although deletion of either NPY or AgRP caused only a modest or nondetectable effect, ablation of both ligands completely abolished the orexigenic action of ghrelin. The authors' results establish an in vivo orexigenic function for NPY and AgRP, mediating the effect of ghrelin.
REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L53 ANSWER 10 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:836057 HCAPLUS
DOCUMENT NUMBER: 140:228109
TITLE: Melanocortin-4 receptor agonists and antagonists: chemistry and potential therapeutic utilities
AUTHOR(S): Sebhat, Iyassu; Ye, Zhixiong; Bednarek, Maria; Weinberg, David; Nargund, Ravi; Fong, Tung M.

CORPORATE SOURCE: Merck Research Laboratories, Rahway, NJ, 07065, USA
SOURCE: Annual Reports in Medicinal Chemistry (2003), 38, 31-40
CODEN: ARMCBI; ISSN: 0065-7743
PUBLISHER: Elsevier Science
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. The development of melanocortin-4 receptor agonists and antagonists was discussed along with their potential application in the treatment of various pathol. conditions, including obesity, erectile dysfunction, inflammatory diseases and central nervous system diseases.
REFERENCE COUNT: 84 THERE ARE 84 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L53 ANSWER 11 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:737487 HCAPLUS
DOCUMENT NUMBER: 139:255386
TITLE: Method using CB1 receptor antagonists and 11β-hydroxysteroid dehydrogenase 1 (11β-HSD1) inhibitors for the treatment or prevention of obesity
INVENTOR(S): Fong, Tung M.; Van Der Ploeg, Leonardus H. T.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 42 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2003075660	A1	20030918	WO 2003-US6031		20030228
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
AU 2003219934	A1	20030922	AU 2003-219934		20030228
EP 1482794	A1	20041208	EP 2003-716219		20030228
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK					
US 2005171161	A1	20050804	US 2003-506395		20030228
PRIORITY APPLN. INFO.:			US 2002-362275P	P	20020306
			WO 2003-US6031	W	20030228

AB The invention provides a method for treating or preventing obesity (or suppressing the appetite) in a human patient by antagonizing CB1 receptors and inhibiting the enzyme 11β-HSD1 in an amount that is effective to treat or prevent obesity. Compds. useful in the invention have an ion channel activity level greater than about 2 μM. Preferably the compound is a dual selective inhibitor, selectively antagonizing CB1 receptors and selectively inhibiting the enzyme 11β-HSD1. Preparation of a series of imidazole derivs. is included.
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L53 ANSWER 12 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:491069 HCAPLUS
DOCUMENT NUMBER: 139:30843
TITLE: Neuropeptide Y Y5 receptor antagonists for treating depression, anxiety, and dementia
INVENTOR(S): MacNeil, Douglas J.; Shearman, Lauren P.; Van der Ploeg, Leonardus H. T.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003051397	A1	20030626	WO 2002-US40012	20021213
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002359706	A1	20030630	AU 2002-359706	20021213
PRIORITY APPLN. INFO.:			US 2001-341542P P	20011217
			WO 2002-US40012 W	20021213

AB The invention relates to the treatment and/or prevention of depression and/or anxiety disorders and/or dementia by the administration of a Neuropeptide Y Y5 antagonist. The invention further provides the use of a medicament for carrying out these methods. Compds. according to the invention include e.g. L-152,804.
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L53 ANSWER 13 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:491037 HCAPLUS
DOCUMENT NUMBER: 139:30867
TITLE: Method using a neuropeptide Y Y5 antagonist for treating circadian rhythm disruptions
INVENTOR(S): MacNeil, Douglas J.; Shearman, Lauren P.; Van der Ploeg, Leonardus H. T.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003051356	A1	20030626	WO 2002-US40015	20021213
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,				

CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2469790	AA	20030626	CA 2002-2469790		20021213
AU 2002351381	A1	20030630	AU 2002-351381		20021213
EP 1463499	A1	20041006	EP 2002-787039		20021213
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK					
US 2005107411	A1	20050519	US 2003-497558		20021213
JP 2005517654	T2	20050616	JP 2003-552289		20021213
PRIORITY APPLN. INFO.:			US 2001-342177P	P	20011217
			WO 2002-US40015	W	20021213

AB A neuropeptide Y Y5 antagonist is useful, alone or in conjunction with other agents, for altering circadian rhythmicity and alleviating circadian rhythm disorders and for enhancing and improving the quality of sleep. The invention further provides the use of a medicament for carrying out these methods. Compds. according to the invention include e.g. L-152,804.

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L53 ANSWER 14 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:261939 HCAPLUS
DOCUMENT NUMBER: 138:281601
TITLE: Methods for the production of melanin-concentrating hormone receptor (MCH-1R) mutants to be used as MCH-1R antagonist binding proteins and screening for compound able to bind to them
INVENTOR(S): Howard, Andrew D.; Pan, Jie; Fong, Tung M.; Marsh, Donald J.; Sailer, Andreas W.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2003027239	A2	20030403	WO 2002-US29931		20020920
WO 2003027239	A3	20041111			
W: CA, JP, US					
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR					
JP 2005508632	T2	20050407	JP 2003-530811		20020920
US 2005069883	A1	20050331	US 2004-488758		20040308
PRIORITY APPLN. INFO.:			US 2001-325129P	P	20010926
			WO 2002-US29931	W	20020920

AB The present invention features MCH-1R antagonist binding proteins, methods for their production and for the screening of compds. that bind them. MCH-1R antagonist binding proteins claimed herein are based on an MCH-1R having one or more alterations to the second intracellular loop or carboxy terminus that render the receptor substantially inactive to MCH binding, either by amino acid substitutions or by the production of fusion proteins.

An MCH-1R antagonist binding protein can bind MCH-1R antagonists, but does not exhibit high affinity MCH binding and is not activated by the MCH.

L53 ANSWER 15 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:133423 HCAPLUS
DOCUMENT NUMBER: 138:182114
TITLE: Protein and cDNA sequence of rat bombesin receptor subtype-3 (BRS-3) and uses thereof in drug screening
INVENTOR(S): Liu, Jie; Fong, Tung M.; Van der Ploeg, Leonardus H. T.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 44 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2003014310	A2	20030220	WO 2002-US24971		20020807
WO 2003014310	A3	20031030			
W: CA, JP, US					
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR					
CA 2456857	AA	20030220	CA 2002-2456857		20020807
EP 1417309	A2	20040512	EP 2002-765952		20020807
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY, TR, BG, CZ, EE, SK					
US 2005222402	A1	20051006	US 2004-486414		20040209
PRIORITY APPLN. INFO.:			US 2001-311014P	P	20010809
			WO 2002-US24971	W	20020807

AB A rat bombesin receptor subtype-3 has been isolated, cloned and sequenced. This receptor is characteristic of the G-protein family of receptors. Rat BRS-3 has seven transmembrane domains (TM 1-7), one N-terminal extracellular domain, one C-terminal intracellular domain and several intracellular loops. Rat and human BRS-3 have different tissue-specific expression patterns and different pharmacol. properties. Surprisingly, rat BRS-3 has an approx. 1000-fold lower affinity to the synthetic peptide ligand dYB than human BRS-3. Such drastic differences result from the variations in the amino acid sequence of the third extracellular loop (E3, amino acid residues 294-311) of the receptor. Thus, a chimeric receptor with the third extracellular loop (E3) of rat BRS-3 switched with the E3 domain of human BRS-3 and other substitution mutants, such as Y298E299S300→S298Q299T300 or D306V307P308→A306M307H308, are described for drug screening. Isolation of rat bombesin receptor subtype-3 may be used to screen and identify novel bombesin receptor modulators that may contribute to the regulation of endocrine processes, metabolism, or the cell cycle. Such compds. may be used in the treatment of conditions that result from deregulated expression of bombesin receptor subtype-3.

L53 ANSWER 16 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:670593 HCAPLUS
DOCUMENT NUMBER: 137:380244
TITLE: A role for the melanocortin 4 receptor in sexual function
AUTHOR(S): Van der Ploeg, Lex H. T.; Martin, William J.; Howard, Andrew D.; Nargund, Ravi P.; Austin, Christopher P.; Guan, Xiaoming; Drisko, Jennifer;

Cashen, Doreen; Sebhat, Iyassu; Patchett, Arthur A.; Figueroa, David J.; DiLella, Anthony G.; Connolly, Brett M.; Weinberg, David H.; Tan, Carina P.; Palyha, Oksana C.; Pong, Sheng-Shung; MacNeil, Tanya; Rosenblum, Charles; Vongs, Aurawan; Tang, Rui; Yu, Hong; Sailer, Andreas W.; Fong, Tung Ming; Huang, Cathy; Tota, Michael R.; Chang, Ray S.; Stearns, Ralph; Tamvakopoulos, Constantin; Christ, George; Drazen, Deborah L.; Spar, Brian D.; Nelson, Randy J.; MacIntyre, D. Euan

CORPORATE SOURCE: Merck Research Laboratories, Rahway, NJ, 07065, USA

SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2002), 99(17), 11381-11386
CODEN: PNASA6; ISSN: 0027-8424

PUBLISHER: National Academy of Sciences

DOCUMENT TYPE: Journal

LANGUAGE: English

AB By using a combination of genetic, pharmacol., and anatomical approaches, we show that the melanocortin 4 receptor (MC4R), implicated in the control of food intake and energy expenditure, also modulates erectile function and sexual behavior. Evidence supporting this notion is based on several findings: (i) a highly selective non-peptide MC4R agonist augments erectile activity initiated by elec. stimulation of the cavernous nerve in wild-type but not MC4R-null mice; (ii) copulatory behavior is enhanced by administration of a selective MC4R agonist and is diminished in mice lacking Mc4r; (iii) reverse transcription (RT)-PCR and non-PCR based methods demonstrate MC4R expression in rat and human penis, and rat spinal cord, hypothalamus, brainstem, pelvic ganglion (major autonomic relay center to the penis), but not in rat primary corpus smooth muscle cavernosum cells; and (iv) in situ hybridization of glans tissue from the human and rat penis reveal MC4R expression in nerve fibers and mechanoreceptors in the glans of the penis. Collectively, these data implicate the MC4R in the modulation of penile erectile function and provide evidence that MC4R-mediated pro-erectile responses may be activated through neuronal circuitry in spinal cord erectile centers and somatosensory afferent nerve terminals of the penis. Our results provide a basis for the existence of MC4R-controlled neuronal pathways that control sexual function.

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L53 ANSWER 17 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:659446 HCAPLUS

DOCUMENT NUMBER: 137:363413

TITLE: Plasma Agouti-related protein level: a possible correlation with fasted and fed states in humans and rats

AUTHOR(S): Shen, C.-P.; Wu, K. K.; Shearman, L. P.; Camacho, R.; Tota, M. R.; Fong, T. M.; Van der Ploeg, L. H. T.

CORPORATE SOURCE: Department of Obesity and Metabolic Research, Merck Research Laboratories, Rahway, NJ, 07065, USA

SOURCE: Journal of Neuroendocrinology (2002), 14(8), 607-610
CODEN: JOUNE2; ISSN: 0953-8194

PUBLISHER: Blackwell Science Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB We measured plasma concns. of agouti-related protein (AGRP) in humans and rats and determined whether these were affected by ingestion of a meal after fasting. In 17 healthy human subjects, the mean plasma concentration of AGRP was

lower in the fed state than in the fasted state. Two hours after a breakfast meal, AGRP levels dropped by 39%. By contrast, a continued fast for 2 h increased the average AGRP concentration by 73%. In rats with diet-induced obesity, refeeding resulted in a 50% decrease in plasma AGRP concns. following a fasting-refeeding protocol. Our results support the notion that plasma AGRP may serve as a biomarker for the transition from a fasted to the satiated state.

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L53 ANSWER 18 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:636043 HCAPLUS
TITLE: "The role of melanocortins in body weight regulation: opportunities for the treatment of obesity"
AUTHOR(S): MacNeil, Douglas J.; Howard, Andrew D.; Guan, Xiaoming; Fong, Tung M.; Nargund, Ravi P.; Bednarek, Maria A.; Goulet, Mark T.; Weinberg, David H.; Strack, Alison M.; Marsh, Donald J.; Chen, Howard Y.; Shen, Chun-Pyn; Chen, Airu S.; Rosenblum, Charles I.; MacNeil, Tanya; Tota, Michael; MacIntyre, Euan D.; Van der Ploeg, Lex H. T.
CORPORATE SOURCE: Merck Research Laboratories, Rahway, NJ, 07065, USA
SOURCE: European Journal of Pharmacology (2002), 450(1), 93-109
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Five G-protein-coupled melanocortin receptors (MC1-MC5) are expressed in mammalian tissues. The melanocortin receptors support diverse physiol. functions, including the regulation of hair color, adrenal function, energy homeostasis, feed efficiency, sebaceous gland lipid production and immune and sexual function. The melanocortins (adrenocorticotropic hormone (ACTH), α-MSH (α-MSH), β-MSH and γ-MSH) are agonist peptide ligands for the melanocortin receptors and these peptides are processed from the pre-prohormone proopiomelanocortin (POMC). Peptide antagonists for the melanocortin MC1, MC3 and MC4 receptors include agouti-related protein (AgRP) and agouti. Diverse lines of evidence, including genetic and pharmacol. data obtained in rodents and humans, support a role for the melanocortin MC3 and MC4 receptors in the regulation of energy homeostasis. Recent advances in the development of potent and selective peptide and non-peptide melanocortin receptor ligands are anticipated to help unravel the roles for the melanocortin receptors in humans and to accelerate the clin. use of small mol. melanocortin mimetics.

REFERENCE COUNT: 152 THERE ARE 152 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L53 ANSWER 19 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:507938 HCAPLUS
DOCUMENT NUMBER: 137:211304
TITLE: Neither agouti-related protein nor neuropeptide Y is critically required for the regulation of energy homeostasis in mice
AUTHOR(S): Qian, Su; Chen, Howard; Weingarth, Drew; Trumbauer, Myrna E.; Novi, Dawn E.; Guan, Xiaoming; Yu, Hong; Shen, Zhu; Feng, Yue; Frazier, Easter; Chen,

Airu; Camacho, Ramon E.; Shearman, Lauren P.; Gopal-Truter, Shobhna; MacNeil, Douglas J.; Van der Ploeg, Lex H. T.; Marsh, Donald J.

CORPORATE SOURCE: Department of Obesity Research, Merck Research Laboratories, Rahway, NJ, 07065, USA
SOURCE: Molecular and Cellular Biology (2002), 22(14), 5027-5035
CODEN: MCEBD4; ISSN: 0270-7306
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Agouti-related protein (AgRP), a neuropeptide abundantly expressed in the arcuate nucleus of the hypothalamus, potently stimulates feeding and body weight gain in rodents. AgRP is believed to exert its effects through the blockade of signaling by α-MSH at central nervous system (CNS) melanocortin-3 receptor (Mc3r) and Mc4r. We generated AgRP-deficient (Agrp-/-) mice to examine the physiol. role of AgRP. Agrp-/- mice are viable and exhibit normal locomotor activity, growth rates, body composition, and food intake. Addnl., Agrp-/- mice display normal responses to starvation, diet-induced obesity, and the administration of exogenous leptin or neuropeptide Y (NPY). In situ hybridization failed to detect altered CNS expression levels for proopiomelanocortin, Mc3r, Mc4r, or NPY mRNAs in Agrp-/- mice. As AgRP and the orexigenic peptide NPY are coexpressed in neurons of the arcuate nucleus, we generated AgRP and NPY double-knockout (Agrp-/-;Npy-/-) mice to determine whether NPY or AgRP plays a compensatory role in Agrp-/- or NPY-deficient (Npy-/-) mice, resp. Similarly to mice deficient in either AgRP or NPY, Agrp-/-;Npy-/- mice suffer no obvious feeding or body weight deficits and maintain a normal response to starvation. Our results demonstrate that neither AgRP nor NPY is a critically required orexigenic factor, suggesting that other pathways capable of regulating energy homeostasis can compensate for the loss of both AgRP and NPY.

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L53 ANSWER 20 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:340765 HCAPLUS
DOCUMENT NUMBER: 137:135141

TITLE: The role of melanocortins in body weight regulation: opportunities for the treatment of obesity

AUTHOR(S): MacNeil, Douglas J.; Howard, Andrew D.; Guan, Xiaoming; Fong, Tung M.; Nargund, Ravi P.; Bednarek, Maria A.; Goulet, Mark T.; Weinberg, David H.; Strack, Alison M.; Marsh, Donald J.; Chen, Howard Y.; Shen, Chun-Pyn; Chen, Airu S.; Rosenblum, Charles I.; MacNeil, Tanya; Tota, Michael; MacIntyre, Euan D.; Van der Ploeg, Lex H. T.
CORPORATE SOURCE: Merck Research Laboratories, Rahway, NJ, 07065, USA

SOURCE: European Journal of Pharmacology (2002), 440(2-3), 141-157
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Five G-protein-coupled melanocortin receptors (MC1-MC5) are expressed in mammalian tissues. The melanocortin receptors support diverse physiol. functions, including the regulation of hair color, adrenal function, energy homeostasis, feed efficiency, sebaceous gland lipid production, and immune and sexual function. The melanocortins (ACTH,

α-MSH, β-MSH, and γ-MSH) are agonist peptide ligands for the melanocortin receptors and these peptides are processed from the pre-prohormone proopiomelanocortin (POMC). Peptide antagonists for the melanocortin MC1, MC3 and MC4 receptors include agouti-related protein (AgRP) and agouti. Diverse lines of evidence, including genetic and pharmacol. data obtained in rodents and humans, support a role for the melanocortin MC3 and MC4 receptors in the regulation of energy homeostasis. Recent advances in the development of potent and selective peptide and non-peptide melanocortin receptor ligands are anticipated to help unravel the roles for the melanocortin receptors in humans and to accelerate the clin. use of small mol. melanocortin mimetics.

REFERENCE COUNT: 152 THERE ARE 152 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L53 ANSWER 21 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:224933 HCAPLUS
DOCUMENT NUMBER: 136:364052
TITLE: Melanin-concentrating hormone 1 receptor-deficient mice are lean, hyperactive, and hyperphagic and have altered metabolism
AUTHOR(S): Marsh, Donald J.; Weingarth, Drew T.; Novi, Dawn E.; Chen, Howard Y.; Trumbauer, Myrna E.; Chen, Airu S.; Guan, Xiao-Ming; Jiang, Michael M.; Feng, Yue; Camacho, Ramon E.; Shen, Zhu; Frazier, Easter G.; Yu, Hong; Metzger, Joseph M.; Kuca, Stephanie J.; Shearman, Lauren P.; Gopal-Truter, Shobhna; MacNeil, Douglas J.; Strack, Alison M.; MacIntyre, D. Euan; Van der Ploeg, Lex H. T.; Qian, Su
CORPORATE SOURCE: Department of Obesity Research, Merck Research Laboratories, Rahway, NJ, 07065, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2002), 99(5), 3240-3245
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Melanin-concentrating hormone (MCH) is a cyclic 19-aa hypothalamic neuropeptide derived from a larger prohormone precursor of MCH (Pmch), which also encodes neuropeptide EI (NEI) and neuropeptide GE (NGE). Pmch-deficient (Pmch-/-) mice are lean, hypophagic, and have an increased metabolic rate. Transgenic mice overexpressing Pmch are hyperphagic and develop mild obesity. Consequently, MCH has been implicated in the regulation of energy homeostasis. The MCH 1 receptor (MCH1R) is one of two recently identified G protein-coupled receptors believed to be responsible for the actions of MCH. The authors evaluated the physiol. role of MCH1R by generating MCH1R-deficient (Mch1r-/-) mice. Mch1r-/- mice have normal body wts., yet are lean and have reduced fat mass. Surprisingly, Mch1r-/- mice are hyperphagic when maintained on regular chow, and their leanness is a consequence of hyperactivity and altered metabolism Consistent with the hyperactivity, Mch1r-/- mice are less susceptible to diet-induced obesity. Importantly, chronic central infusions of MCH induce hyperphagia and mild obesity in wild-type mice, but not in Mch1r-/- mice. The authors conclude that MCH1R is a physiol. relevant MCH receptor in mice that plays a role in energy homeostasis through multiple actions on locomotor activity, metabolism, appetite, and neuroendocrine function.

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L53 ANSWER 22 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:640003 HCAPLUS
TITLE: L-166,446, a second generation growth hormone secretagogue
AUTHOR(S): Nargund, R. P.; Ye, Z.; Tata, J.; Lu, Z.; Barakat, K.; Hong, Q.; Bakshi, R.; Gao, Y.; Tamvakopoulos, C.; Colwell, L.; Feighner, S.; Hreniuk, D.; Pong, S.; Cheng, K.; Schleim, K.; Jacks, T.; Strack, A.; Hickey, G.; Howard, A.; Van der Ploeg, L.; Bailey, A.; Smith, R.; Patchett, A. A.
CORPORATE SOURCE: Medicinal Chemistry, Merck Research Laboratories, Rahway, NJ, 07065, USA
SOURCE: Abstracts of Papers, 222nd ACS National Meeting, Chicago, IL, United States, August 26-30, 2001 (2001), MEDI-184. American Chemical Society: Washington, D. C.
CODEN: 69BUZP
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB L-166,446 is a potent agonist (EC50=2.1nM) of the human GH secretagogue receptor with high oral bioavailability in dogs (>60%). It is significantly more potent than MK-0677 for releasing GH in dogs. Plasma GH concns. were increased in beagles with i.v. doses as low as 1 μg/kg and with oral doses of 15.6 μg/kg or greater. Furthermore, L-166,446 potently stimulates food intake in rats following i.v. administration. Receptor mutagenesis and modeling studies are being carried out to evaluate the binding modes of L-166,446, MK-0677 and the recently disclosed endogenous ligand ghrelin. This lecture will describe the design and biol. profile of L-166,446.

L53 ANSWER 23 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:639970 HCAPLUS
TITLE: Design and biological profile for selective agonists for the melanocortin subtype-4 receptor
AUTHOR(S): Nargund, R. P.; Sebhat, I.; Ye, Z.; Barakat, K.; Weinberg, D.; MacNeil, T.; Kalyani, R.; Martin, W.; Cashen, D.; Chen, H.; Drisko, J.; Mosley, R.; Fong, T.; Stearns, R.; Miller, R.; Tamvakopoulos, R.; Colwell, L.; Strack, A.; Shen, Xiaolan; Tan, Carina; Pong, Sheng-Shung; Howard, A.; Sailer, A.; Hickey, G.; MacIntyre, E.; Van der Ploeg, L.; Patchett, A.
CORPORATE SOURCE: Medicinal Chemistry, Merck Research Laboratories, Rahway, NJ, 07065, USA
SOURCE: Abstracts of Papers, 222nd ACS National Meeting, Chicago, IL, United States, August 26-30, 2001 (2001), MEDI-151. American Chemical Society: Washington, D. C.
CODEN: 69BUZP
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB The design of selective agonists of the melanocortin subtype-4 receptor (MC4R) is of considerable interest since MC4R agonists may be useful for the treatment of obesity and related co-morbidities. Recent studies indicate that the non-selective peptide agonist melanotan II (MT-II) promotes erectile function in humans through an unknown mechanism. This lecture will describe the design and biol. profile of Compound A, a non-peptide, full agonist of rodent and human MC4Rs. Our results suggest that the activation of MC4R can affect appetite and can stimulate erectile function.

L53 ANSWER 24 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:518634 HCAPLUS
DOCUMENT NUMBER: 135:326950
TITLE: Spiro(indoline-3,4'-piperidine) growth hormone secretagogues as ghrelin mimetics
AUTHOR(S): Palucki, B. L.; Feighner, S. D.; Pong, S.-S.; McKee, K. K.; Hreniuk, D. L.; Tan, C.; Howard, A. D.; Van der Ploeg, L. H. Y.; Patchett, A. A.; Nargund, R. P.
CORPORATE SOURCE: Department of Medicinal Chemistry, Merck Research Laboratories, Rahway, NJ, 07065, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (2001), 11(14), 1955-1957
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A series of small mols. derived from MK-0677, a potent synthetic GHS, mimicking the N-terminal Gly-Ser-O-(n-octanoyl)-L-Ser-Phe segment of ghrelin was synthesized and tested in a binding and in a functional assay measuring intracellular calcium elevation in HEK-293 cells expressing hGHSR1a. Replacement of Phe in this tetrapeptide with a spiro(indoline-3,4'-piperidine) group, Gly-Ser with 2-aminoisobutyric acid, and O-(n-octanoyl)-L-Ser with O-benzyl-D-Ser provided synthetic GHS agonists with similar functional potency as ghrelin.
REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L53 ANSWER 25 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:359730 HCAPLUS
DOCUMENT NUMBER: 135:1225
TITLE: Melanocortin-4 receptor deficient cells and non-human transgenic animals and methods of selecting compounds which regulate body weight
INVENTOR(S): Van Der Ploeg, Leonardus H. T.; Chen, Airu S.; Chen, Howard Y.; Forrest, Michael J.; MacIntyre, Duncan E.; Metzger, Joseph M.; Palyha, Oksana C.; Feighner, Scott D.; Hreniuk, Donna
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 58 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2001033956	A1	20010517	WO 2000-US31061		20001113
W: CA, JP, US					
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR					
CA 2390740	AA	20010517	CA 2000-2390740		20001113
EP 1241934	A1	20020925	EP 2000-980352		20001113
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY, TR					
JP 2003525596	T2	20030902	JP 2001-535977		20001113
US 2005034185	A1	20050210	US 2003-603249		20030625
PRIORITY APPLN. INFO.:			US 1999-165074P	P	19991112

US 1999-165141P P 19991112
US 2000-220713P P 20000726
US 2000-709066 A3 20001109
WO 2000-US31061 W 20001113

AB Cells and non-human transgenic animals have been engineered to be deficient in the gene encoding the melanocortin-4 receptor protein (MC-4R). Male MC-4R deficient transgenic animals of the present invention show increased fat mass and are obese, while female heterozygous MC-4R deficient transgenic animals have similar body weight to wild type mice. These MC-4R deficient transgenic animals can be used to select for and test potential modulators (e.g., agonists or antagonists) of MC-4R which control food intake and metabolic rate. This data allows for methods of screening for preferential MC-4R modulators which effect body weight through modulation of both metabolic rate and food intake, as well as associated methods of treating various disorders associated with inappropriate regulation of body weight The present invention especially related to anal. of the complex function(s) of MC-4R as related to obesity and diabetes by generating knockout transgenic mice and studying how various potential modulators interact within these manipulated animals. An aequorin bioluminescence assay is provided that uses promiscuous Gα protein in Xenopus laevis oocytes to measure MC-4R activity.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L53 ANSWER 26 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:359728 HCAPLUS
DOCUMENT NUMBER: 134:362227
TITLE: Melanocortin-3 receptor deficient cells and non-human transgenic animals and methods of selecting compounds which regulate body weight
INVENTOR(S): Van Der Ploeg, Leonardus H. T.; Chen, Howard Y.; Chen, Airu S.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 100 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001033954	A1	20010517	WO 2000-US30746	20001109
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2390723	AA	20010517	CA 2000-2390723	20001109
AU 2001017584	A5	20010606	AU 2001-17584	20001109
EP 1241933	A1	20020925	EP 2000-980304	20001109
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2003513645	T2	20030415	JP 2001-535975	20001109
US 6639123	B1	20031028	US 2000-709066	20001109

US 2005034185	A1	20050210	US 2003-603249		20030625
PRIORITY APPLN. INFO.:			US 1999-165074P	P	19991112
			US 1999-165141P	P	19991112
			US 2000-220713P	P	20000726
			US 2000-709066	A3	20001109
			WO 2000-US30746	W	20001109

AB Cells and non-human transgenic animals have been engineered to be deficient in the gene encoding the melanocortin-3 receptor protein (MC-3R). MC-3R deficient transgenic animals have increased fat mass and reduced lean body mass, showing that the MC-3R protein is involved in the regulation of body fat and muscle mass. These MC-3R deficient transgenic animals can be used to select for and test potential modulators of MC-3R. This data allows for methods of screening for MC-3R modulators which effect body weight and associated methods of treating various disorders associated with inappropriate regulation of body weight The disclosure also relates to a MC-3R/MC-4R double knockout mouse which can be used to select for and test potential modulators (e.g., agonists or antagonists) of MC-3R and/or MC-4R. It is shown that MC-3R serves a non-redundant role, when compared to MC-4R, in the regulation of energy homeostasis.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L53 ANSWER 27 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2001:241476 HCAPLUS

DOCUMENT NUMBER: 134:321200

TITLE: Differential regulation of neuropeptide Y receptors in the brains of NPY knock-out mice

AUTHOR(S): Trivedi, P. G.; Yu, H.; Trumbauer, M.; Chen, H.; Van der Ploeg, L. H. T.; Guan, X.-M.

CORPORATE SOURCE: Department of Obesity Research, Merck Research Laboratories, Rahway, NJ, 07065, USA

SOURCE: Peptides (New York, NY, United States) (2001), 22(3), 395-403
CODEN: PPTDD5; ISSN: 0196-9781

PUBLISHER: Elsevier Science Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB To study the effect of NPY deletion on the regulation of its receptors in the NPY knockout (NPY KO) mice, the expression and binding of NPY receptors were investigated by in situ hybridization and receptor autoradiog. using 125I-[Leu31,Pro34]PYY and 125I-PYY3-36 as radioligands. A 6-fold increase in Y2 receptor mRNA was observed in the CA1 region of the hippocampus in NPY KO mice, but a significant change could not be detected for Y1, Y4, Y5 and y6 receptors. Receptor binding reveals a 60-400% increase of Y2 receptor binding in multiple brain areas. A similar increase in Y1 receptor binding was seen only in the hypothalamus. These results demonstrate the NPY receptor expression is altered in mice deficient for its natural ligand.

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L53 ANSWER 28 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2001:146724 HCAPLUS

DOCUMENT NUMBER: 135:133455

TITLE: Orphan G-protein-coupled receptors and natural ligand discovery

AUTHOR(S): Howard, A. D.; McAllister, G.; Feighner, S. D.; Liu, Q.; Nargund, R. P.; Van der Ploeg, L.

H. T.; Patchett, A. A.
CORPORATE SOURCE: Dept of Metabolic Disorders, Merck Research Laboratories, Rahway, NJ, 07065, USA
SOURCE: Trends in Pharmacological Sciences (2001), 22(3), 132-140
CODEN: TPHSDY; ISSN: 0165-6147
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with 104 refs. The superfamily of 7-transmembrane-domain G-protein-coupled receptors (GPCRs) is the largest and most diverse group of transmembrane proteins involved in signal transduction. Each of the .apprx.1000 family members found in vertebrates responds to stimuli as diverse as hormones, neurotransmitters, odorants, and light, which selectively activate intracellular signaling events mediated by heterotrimeric G proteins. Because GPCRs are centrally positioned in the plasma membrane to initiate a cascade of cellular responses by diverse extracellular mediators, it is not surprising that modulation of GPCR function has been successful in the development of many marketed therapeutic agents. It has become clear that GPCRs for which a natural activating ligand has not yet been identified (orphan GPCRs) might provide a path to discovering new cellular substances that are important in human physiol. The process of de-orphanizing these novel proteins has accelerated significantly and opened up new avenues for research in human physiol. and pharmacol.
REFERENCE COUNT: 104 THERE ARE 104 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L53 ANSWER 29 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:880962 HCAPLUS
DOCUMENT NUMBER: 134:42445
TITLE: Preparation of piperidine amino acid derivatives as melanocortin-4 receptor agonists
INVENTOR(S): Bakshi, Raman K.; Barakat, Khaled J.; Nargund, Ravi P.; Palucki, Brenda L.; Patchett, Arthur A.; Sebhat, Iyassu; Ye, Zhixiong; Van, Der Ploeg Leonardus H. T.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA; Van Der Ploeg, Leonardus H. T.
SOURCE: PCT Int. Appl., 124 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000074679	A1	20001214	WO 2000-US14930	20000531
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2377369	AA	20001214	CA 2000-2377369	20000531
EP 1187614	A1	20020320	EP 2000-937961	20000531
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,				

	IE, SI, LT, LV, FI, RO				
JP 2003505435	T2	20030212	JP 2001-512328		20000531
AU 766191	B2	20031009	AU 2000-53068		20000531
US 6350760	B1	20020226	US 2000-585111		20000601
US 2002137664	A1	20020926	US 2001-990499		20011121
AU 2003248456	A1	20031106	AU 2003-248456		20030929
PRIORITY APPLN. INFO.:			US 1999-137477P	P	19990604
			US 1999-169209P	P	19991202
			WO 2000-US14930	W	20000531
			US 2000-585111	A3	20000601

OTHER SOURCE(S): MARPAT 134:42445
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Piperidine derivs. I [R2C2 = aryl, 5- or 6-membered heteroaryl or heterocyclyl, 5- to 7-membered carbocyclyl, which may be substituted; L = (CRb2)m, where Rb = H, alkyl, (CH2)n-cycloalkyl or -aryl; m = 0-2, n = 0-3; X, Y = (CH2)0-2; Ra = H, alkyl, (CHRb)n-cycloalkyl, -aryl, -heteroaryl, -O(CHRb)naryl, which may be substituted; Re = H, alkyl, (CH2)n-aryl, -cycloalkyl, -heteroaryl, which may be substituted, acyl, sulfonyl, etc.; R1 = H, alkyl, (CH2)n-cycloalkyl, -aryl, -heteroaryl, -heterocyclyl; R2 = any group given for R1, CN, (CH2)n-carboxamido, -carboxy, -acylamino, sulfonylamino, -amino, etc.] were prepared as agonists of the human melanocortin receptors, in particular, the human melanocortin-4 receptor (MC-4R). They are therefore useful for the treatment, control, or prevention of diseases and disorders responsive to the activation of MC-4R, such as obesity, diabetes, sexual dysfunction, including erectile dysfunction and female sexual dysfunction. Thus, II trifluoroacetate, prepared by coupling of Et 1-(D-4-chlorophenylalanyl)-4-cyclohexyl-4-[(1,2,4-triazol-1-yl)methyl]piperidine trifluoroacetate (preparation given) with N-tert-butoxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Boc-D-Tic), was > 2,200-fold, > 10,000-fold, and > 580-fold selective for the human MC-4R over human MC-1R, MC-2R, and MC-3R, resp.

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L53 ANSWER 30 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:666775 HCAPLUS
DOCUMENT NUMBER: 133:218143
TITLE: Isoforms of mouse serotonin 5-HT2c receptor
INVENTOR(S): Fong, Tung M.; Liu, Jie; Van Der Ploeg, Leonardus H. T.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000055205	A1	20000921	WO 2000-US6396	20000310
W: CA, JP, US				

RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

CA 2364571	AA	20000921	CA 2000-2364571	20000310
EP 1163269	A1	20011219	EP 2000-917857	20000310
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
US 6495665	B1	20021217	US 2000-526309	20000315
US 2003109685	A1	20030612	US 2002-280858	20021217
US 6835548	B2	20041228		
PRIORITY APPLN. INFO.:			US 1999-124439P	P 19990315
			WO 2000-US6396	W 20000310
			US 2000-526309	A3 20000315

AB The invention includes mouse serotonin 5-HT2c receptor isoforms having amino acid replacements at one or more positions of the natural mouse serotonin 5-HT2c receptor polypeptide sequence, specifically at one or more of positions 157, 159 and 161. The polypeptides are useful for identifying ligands which bind with the serotonin 5-HT2c receptor and modulators of the serotonin 5-HT2c, and for identifying drugs with affinity for 5-HT2 receptors which are used to treat schizophrenia, Parkinsonism, and anxiety disorders. The invention also includes isolated or purified isoforms, DNA encoding the isoforms, and expression vectors encoding the receptor isoforms.

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L53 ANSWER 31 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2000:646802 HCAPLUS
DOCUMENT NUMBER: 133:332799
TITLE: Inactivation of the mouse melanocortin-3 receptor results in increased fat mass and reduced lean body mass
AUTHOR(S): Chen, Airu S.; Marsh, Donald J.; Trumbauer, Myrna E.; Frazier, Easter G.; Guan, Xiao-Ming; Yu, Hong; Rosenblum, Charles I.; Vongs, Aurawan; Feng, Yue; Cao, Linhai; Metzger, Joseph M.; Strack, Alison M.; Camacho, Ramon E.; Mellin, Theodore N.; Nunes, Christian N.; Min, William; Fisher, Jill; Gopal-Truter, Shobhna; MacIntyre, D. Euan; Chen, Howard Y.; Van der Ploeg, Lex H. T.
CORPORATE SOURCE: Department of Obesity Research, Merck Research Laboratories, Rahway, NJ, USA
SOURCE: Nature Genetics (2000), 26(1), 97-102
CODEN: NGENEC; ISSN: 1061-4036
PUBLISHER: Nature America Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Genetic and pharmacol. studies have defined a role for the melanocortin-4 receptor (Mc4r) in the regulation of energy homeostasis. The physiol. function of Mc3r, a melanocortin receptor expressed at high levels in the hypothalamus, has remained unknown. We evaluated the potential role of Mc3r in energy homeostasis by studying Mc3r-deficient (Mc3r-/-) mice and compared the functions of Mc3r and Mc4r in mice deficient for both genes. The 4-6-mo Mc3r-/- mice have increased fat mass, reduced lean mass and higher feed efficiency than wild-type littermates, despite being hypophagic and maintaining normal metabolic rates. Feed efficiency is the ratio of weight gain to food intake. Consistent with increased fat mass, Mc3r-/- mice are hyperleptinemic and male Mc3r-/- mice develop mild hyperinsulinemia. Mc3r-/- mice did not have significantly altered corticosterone or total thyroxine (T4) levels. Mice lacking both Mc3r and Mc4r become significantly heavier than Mc4r-/- mice. We conclude that

Mc3r and Mc4r serve non-redundant roles in the regulation of energy homeostasis.

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L53 ANSWER 32 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:584002 HCAPLUS
DOCUMENT NUMBER: 134:51805
TITLE: Role of the melanocortin-4 receptor in metabolic rate and food intake in mice
AUTHOR(S): Chen, Airu S.; Metzger, Joseph M.; Trumbauer, Myrna E.; Guan, Xiao-Ming; Yu, Hong; Frazier, Easter G.; Marsh, Donald J.; Forrest, Michael J.; Gopal-Truter, Shobhna; Fisher, Jill; Camacho, Ramon E.; Strack, Alison M.; Mellin, Theodore N.; MacIntyre, D. Euan; Chen, Howard Y.; Van der Ploeg, Lex H. T.
CORPORATE SOURCE: Merck Research Laboratories, Department of Metabolic Disorders, NJ, USA
SOURCE: Transgenic Research (2000), 9(2), 145-154
CODEN: TRSEES; ISSN: 0962-8819
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We evaluated the role of the melanocortin-4 receptor (MC-4R) in the control of metabolic rate and food intake in mice. I.p. administration of the non-selective MC-R agonist melanotan II (MT-II; a cyclic heptapeptide) increases metabolic rate in wild-type mice, while MC-4R knockout mice are insensitive to the effects of MT-II on metabolic rate. MC-4R knockout mice are also insensitive to the effects of MT-II on reducing food intake. We conclude that MC-4R can mediate control of both metabolic rate and food intake in mice. We infer that a role for MC-3R in mediating the acute effects of MT-II on basal metabolic rate and food intake in wild-type mice seems limited.
REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L53 ANSWER 33 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:457087 HCAPLUS
DOCUMENT NUMBER: 133:84749
TITLE: DNA molecules encoding a splice variant of human melanocortin 1 receptor protein
INVENTOR(S): Howard, Andrew D.; Macneil, Douglas J.; Van der Ploeg, Leonardus H. T.
PATENT ASSIGNEE(S): Merck and Co., Inc., USA
SOURCE: PCT Int. Appl., 101 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000039147	A1	20000706	WO 1999-US29963	19991216
W: CA, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2357036	AA	20000706	CA 1999-2357036	19991216
EP 1140968	A1	20011010	EP 1999-963099	19991216

EP 1140968	B1	20060412			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY					
JP 2002533111	T2	20021008	JP 2000-591058		19991216
AT 323106	E	20060415	AT 1999-963099		19991216
US 6693184	B1	20040217	US 2001-868552		20010618
PRIORITY APPLN. INFO.:			US 1998-113401P	P	19981223
			WO 1999-US29963	W	19991216

AB The present invention relates to DNA mols. encoding splice variants of the melanocortin-1 receptor (MC-R1) protein belonging to the rhodopsin subfamily of G-protein coupled receptors. The human type B MC-R1 nucleic acids comprise a 3'-exon segment which encodes a 65-amino acid C-terminal extension. Multiple polymorphisms of human MCR-1B are identified. The pharmacol. properties of MCR-1B are also identified. Recombinant vectors comprising DNA mols. encoding MC-R1B protein, recombinant host cells which contain a recombinant vector encoding MC-R1B, the human MC-R1B protein encoded by the DNA mol., and methods of identifying selective agonists and antagonists of MC-R1B proteins are disclosed.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L53 ANSWER 34 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2000:335526 HCAPLUS
DOCUMENT NUMBER: 132:343822
TITLE: Rhesus monkey (Macaca mulatta) melanocortin 5 receptor (MC-5R), its sequence, cDNA encoding it, recombinant production and use in methods designed to identify agonists and/or antagonists
INVENTOR(S): Fong, Tung M.; Van Der Ploeg, Leonardus H. T.; Huang, Ruey-Ruey C.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 57 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2000028002	A1	20000518	WO 1999-US25755		19991105
W: CA, JP, US					
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE					
CA 2349848	AA	20000518	CA 1999-2349848		19991105
EP 1137757	A1	20011004	EP 1999-956857		19991105
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI					
JP 2002529075	T2	20020910	JP 2000-581169		19991105
US 6645738	B1	20031111	US 2001-831228		20010504
PRIORITY APPLN. INFO.:			US 1998-107632P	P	19981109
			WO 1999-US25755	W	19991105

AB The invention provides a nucleic acid mol. (cDNA) encoding the rhesus monkey (Macaca mulatta) melanocortin-5 receptor (MC-5R). The invention also provides an expression vector (eukaryotic or prokaryotic) containing the MC-5R cDNA mol. and host cells transformed with said vector, used for the recombinant production of MC-5R. The invention further provides anti-MC-5R antibodies. Still further, the invention provides methods for identifying substances that bind and/or modulate MC-5R, which include potential agonists and/or antagonists of MC-5R. The methods are cell based whereby

an expression vector containing polynucleotides encoding MC-5R is transfected into a host cell, allowing for the recombinant production of MC-5R prior to addition of the test substance. Finally, the invention provides the cDNA sequence, as well as the corresponding amino acid sequence of rhesus monkey MC-5R. The invention demonstrated the use of CHO cells in the recombinant production of MC-5R and used this expression system to study the pharmacol. properties of rhesus monkey MC-5R. The invention showed the binding affinity (IC50) and activation potency (EC50) of a number of peptides (Shu-9119, NDP, α-MSH, γ2-MSH, ACTH1-24, and MT-II) for rhesus monkey and human MC-5Rs.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L53 ANSWER 35 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:335427 HCAPLUS
DOCUMENT NUMBER: 132:330639
TITLE: Protein and cDNA sequences of Macaca mulatta melanocortin-4 receptor, and uses thereof in drug screening applications
INVENTOR(S): Macneil, Douglas J.; Weinberg, David H.; Van Der Ploeg, Leonardus H. T.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 53 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000027863	A1	20000518	WO 1999-US25767	19991105
W: CA, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2350169	AA	20000518	CA 1999-2350169	19991105
EP 1129105	A1	20010905	EP 1999-971813	19991105
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2003521875	T2	20030722	JP 2000-581040	19991105
US 6573070	B1	20030603	US 2001-831206	20010504
US 2003166009	A1	20030904	US 2003-373355	20030225
US 7029865	B2	20060418		

PRIORITY APPLN. INFO.:

US 1998-107721P	P	19981109
WO 1999-US25767	W	19991105
US 2001-831206	A3	20010504

AB The invention provides protein and cDNA sequences of rhesus monkey (Macaca mulatta) melanocortin-4 receptor. The invention also relates to recombinant vectors comprising DNA mols. encoding rhesus MC-4R, host cells which contain said recombinant vectors, and methods of identifying selective agonists and antagonists of rhesus MC-4R.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L53 ANSWER 36 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:335426 HCAPLUS
DOCUMENT NUMBER: 132:344130
TITLE: Protein and cDNA sequences of Macaca mulatta melanocortin-3 receptor, and uses thereof in drug screening applications

INVENTOR(S): Fong, Tung M.; Van Der Ploeg, Leonardus H. T.; Huang, Ruey-Ruey C.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000027862	A1	20000518	WO 1999-US25747	19991105
W: CA, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2349950	AA	20000518	CA 1999-2349950	19991105
EP 1129104	A1	20010905	EP 1999-971812	19991105
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2002542760	T2	20021217	JP 2000-581039	19991105

PRIORITY APPLN. INFO.: US 1998-107725P P 19981109
WO 1999-US25747 W 19991105

AB The invention provides protein and cDNA sequences of rhesus monkey (Macaca mulatta) melanocortin-3 receptor. The invention also relates to recombinant vectors comprising DNA mols. encoding rhesus MC-3R, host cells which contain said recombinant vectors, and methods of identifying selective agonists and antagonists of rhesus MC-3R.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L53 ANSWER 37 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:189667 HCAPLUS
DOCUMENT NUMBER: 133:1003
TITLE: A melanocortin agonist reduces neuronal firing rate in rat hypothalamic slices
AUTHOR(S): Fong, T. M.; Van der Ploeg, L. H. T.
CORPORATE SOURCE: R80M-213, Department of Obesity Research, Merck Research Laboratories, Rahway, NJ, USA
SOURCE: Neuroscience Letters (2000), 283(1), 5-8
CODEN: NELED5; ISSN: 0304-3940
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Bath application of α-MSH to rat hypothalamic slices inhibited the spontaneous firing rate of continuously firing neurons in the ventromedial hypothalamic nucleus or paraventricular nucleus. This inhibitory effect is most likely direct and independent of synaptic transmission. The α-MSH-responsive neurons tested did not respond to neuropeptide Y (NPY) application. α-MSH did not inhibit the intraburst firing rate of phasic bursting neurons, although these bursting neurons were highly responsive to a serotonin 5HT2a/2b/2c agonist with a change of firing pattern to continuous firing and an increase in firing rate which was reversed by NPY. These results suggest that a change of neuronal firing rate may represent a neural correlate of satiety induced by anorexic agents.

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L53 ANSWER 38 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2000:160630 HCAPLUS
DOCUMENT NUMBER: 132:303587
TITLE: Species-dependent pharmacological properties of the melanocortin-5 receptor
AUTHOR(S): Huang, R.-R. C.; Singh, G.; Van der Ploeg, L. H. T.; Fong, T. M.
CORPORATE SOURCE: Department of Obesity Research, Merck Research Laboratories, Rahway, NJ, 07065, USA
SOURCE: Journal of Receptor and Signal Transduction Research (2000), 20(1), 47-59
CODEN: JRETET; ISSN: 1079-9893
PUBLISHER: Marcel Dekker, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The genes encoding the melanocortin-3 receptor and melanocortin-5 receptor have been cloned from rhesus monkey. Heterologous expression in CHO cells indicated species dependent in vitro pharmacol. properties for the human and rhesus melanocortin-5 receptors. Several peptides including NDP-α-MSH, α-MSH, MT-II and ACTH 1-24 are more potent at the rhesus melanocortin-5 receptor than the human melanocortin-5 receptor by more than 10-fold. In contrast, the authors found no species difference in pharmacol. properties between the human and rhesus melanocortin-3 receptors. Such a species-dependent pharmacol. difference for melanocortin-5 receptor appears to be an exception compared to other G protein-coupled receptors from human and rhesus monkey.

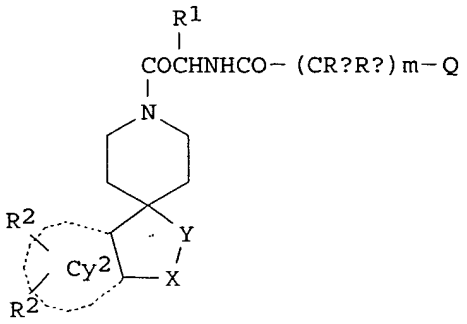
REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L53 ANSWER 39 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:795654 HCAPLUS
DOCUMENT NUMBER: 132:22957
TITLE: Preparation of spiropiperidine derivatives as melanocortin receptor agonists
INVENTOR(S): Nargund, Ravi P.; Ye, Zhixiong; Palucki, Brenda L.; Bakshi, Raman K.; Patchett, Arthur A.; Van Der Ploeg, Leonardus H. T.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 77 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9964002	A1	19991216	WO 1999-US13252	19990610
W: AE, AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2334551	AA	19991216	CA 1999-2334551	19990610
AU 9946801	A1	19991230	AU 1999-46801	19990610
AU 742425	B2	20020103		
EP 1085869	A1	20010328	EP 1999-930220	19990610
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, LT, LV, FI, RO				

US 6294534	B1	20010925	US 1999-329814		19990610
JP 2002517444	T2	20020618	JP 2000-553071		19990610
US 2001029259	A1	20011011	US 2001-781373		20010212
US 6410548	B2	20020625			
PRIORITY APPLN. INFO.:			US 1998-88908P	P	19980611
			GB 1998-17179	A	19980806
			US 1999-123260P	P	19990308
			US 1999-329814	A3	19990610
			WO 1999-US13252	W	19990610

OTHER SOURCE(S): MARPAT 132:22957
GI



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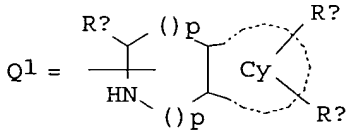


AB Certain novel spiropiperidine compds. I [Cy2 = six-membered aromatic ring containing 0 or 1 N; X = O, CH2, etc.; Q = Q1; Y = CO, SO2, etc; R1, Rb = H, C1-8 alkyl, etc.; R2 = H or halo; Rc = Rb, halo, ORb, NHSO2Rb, N(Rb)2, SO2Rb, CF3, OCF3; Cy = aryl, 5 or 6 membered heteroaryl, 5 or 6 membered heterocyclyl, 5 or 6 membered carbocyclyl; m, p, q independently = 0, 1, or 2] are agonists of melanocortin receptors (no data) and are useful for the treatment, control or prevention of diseases and disorders responsive to the activation of melanocortin receptors. The compds. of the present invention are therefore useful for treatment of diseases and disorders such as obesity, diabetes, sexual dysfunction including erectile dysfunction and female sexual dysfunction.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L53 ANSWER 40 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:693308 HCAPLUS
DOCUMENT NUMBER: 132:511
TITLE: Use of bioluminescent aequorin for the pharmacological characterization of 5HT receptors

AUTHOR(S): Schaeffer, M.-T.; Cully, D.; Chou, M.; Liu, J.; Van der Ploeg, L. H. T.; Fong, T. M.
CORPORATE SOURCE: Merck Research Laboratories, Rahway, NJ, 07065, USA
SOURCE: Journal of Receptor and Signal Transduction Research (1999), 19(6), 927-938
CODEN: JRETET; ISSN: 1079-9893
PUBLISHER: Marcel Dekker, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A convenient functional assay for 5HT2a and 5HT2c receptors is reported utilizing the bioluminescent aequorin to detect intracellular calcium changes. Using this assay, the pharmacol. properties of many 5HT ligands can be determined in a 96-well format. The data indicate that the aequorin detection method is superior to the inositol phosphate assay with regard to speed and scope. This system is also appropriate for kinetic studies of receptor desensitization. We showed that the human 5HT2c receptor desensitizes in a biphasic manner, with a fast desensitization of approx. 90% of the total response occurring within 15 min while the remaining 10% response remains for at least 3 h.

REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L53 ANSWER 41 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:426503 HCAPLUS
DOCUMENT NUMBER: 131:194440
TITLE: Receptor for motilin identified in the human gastrointestinal system
AUTHOR(S): Feighner, Scott D.; Tan, Carina P.; McKee, Karen Kulju; Palyha, Oksana C.; Hreniuk, Donna L.; Pong, Sheng-Shung; Austin, Christopher P.; Figueroa, David; MacNeil, Douglas; Cascieri, Margaret A.; Nargund, Ravi; Bakshi, Raman; Abramovitz, Mark; Stocco, Rino; Kargman, Stacia; O'Neill, Gary; Van Der Ploeg, Lex H. T.; Evans, Jilly; Patchett, Arthur A.; Smith, Roy G.; Howard, Andrew D.
CORPORATE SOURCE: Department of Metabolic Disorders, Department of Medicinal Chemistry, Merck Research Laboratories, Rahway, NJ, 07065, USA
SOURCE: Science (Washington, D. C.) (1999), 284(5423), 2184-2188
CODEN: SCIEAS; ISSN: 0036-8075
PUBLISHER: American Association for the Advancement of Science
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Motilin is a 22-amino acid peptide hormone expressed throughout the gastrointestinal (GI) tract of humans and other species. It affects gastric motility by stimulating interdigestive antrum and duodenal contractions. A heterotrimeric guanosine triphosphate-binding protein (G protein)-coupled receptor for motilin was isolated from human stomach, and its amino acid sequence was found to be 52 percent identical to the human receptor for growth hormone secretagogues. The macrolide antibiotic erythromycin also interacted with the cloned motilin receptor, providing a mol. basis for its effects on the human gastrointestinal tract. The motilin receptor is expressed in enteric neurons of the human duodenum and colon. Development of motilin receptor agonists and antagonists may be useful in the treatment of multiple disorders of gastrointestinal motility.

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L53 ANSWER 42 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:405171 HCAPLUS
DOCUMENT NUMBER: 131:54344
TITLE: C-terminal region of agouti-related transcript (ART) protein for melanocortin and MSH assays
INVENTOR(S): Fong, Tung Ming; Van der Ploeg, Leonardus H. T.; Tota, Michael R.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 53 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 9931508	A1	19990624	WO 1998-US26457		19981211
W: CA, JP, US					
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE					
CA 2314971	AA	19990624	CA 1998-2314971		19981211
EP 1040351	A1	20001004	EP 1998-963882		19981211
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI					
JP 2002508194	T2	20020319	JP 2000-539354		19981211
US 6878520	B1	20050412	US 2000-581894		19981211
PRIORITY APPLN. INFO.:			US 1997-69747P	P	19971216
			WO 1998-US26457	W	19981211

AB Novel polypeptides derived from the C-terminal region of the human and mouse agouti-related transcript (ART) proteins are provided. Also provided are DNA sequences encoding the novel C-terminal polypeptides. The novel C-terminal polypeptides can be used to inhibit the binding of melanocyte-stimulating hormones to melanocortin receptors. Methods of identifying inhibitors of the binding of ART protein to melanocortin receptors are also provided.
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L53 ANSWER 43 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:188761 HCAPLUS
DOCUMENT NUMBER: 130:336370
TITLE: Age-related cognitive deficits, impaired long-term potentiation and reduction in synaptic marker density in mice lacking the β-amyloid precursor protein
AUTHOR(S): Dawson, G. R.; Seabrook, G. R.; Zheng, H.; Smith, D. W.; Graham, S.; O'Dowd, G.; Bowery, B. J.; Boyce, S.; Trumbauer, M. E.; Chen, H. Y.; Van Der Ploeg, L. H. T.; Sirinathsinghji, D. J. S.
CORPORATE SOURCE: Merck Sharp and Dohme Research Laboratories, Neuroscience Research Centre, Essex, CM20 2QR, UK
SOURCE: Neuroscience (Oxford) (1999), 90(1), 1-13
CODEN: NRSCDN; ISSN: 0306-4522
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Mutations in the β-amyloid precursor protein are strongly associated with some cases of familial Alzheimer's disease. The normal physiol. role of β-amyloid precursor protein in the brain was evaluated in a cross-sectional anal. of mice deficient in β-amyloid precursor protein. Compared with wild-type control mice the β-amyloid

precursor protein-null mice developed age-dependent deficits in cognitive function and also had impairments in long-term potentiation. In addition, the brains of the β-amyloid precursor protein-null mice had marked reactive gliosis in many areas, especially in the cortex and hippocampus. A subpopulation of mice died prematurely (between three and 18 mo of age). Anal. of another six mice from the same population that were showing weight loss and hypolocomotor activity exhibited a marked reactive gliosis as detected by immunoreactivity for glial fibrillary acidic protein and a profound loss of immunoreactivities for the presynaptic terminal vesicle marker proteins synaptophysin and synapsin and the dendritic marker microtubule-associated protein-2 in many brain areas, but most predominantly in the cortex and hippocampus. These results suggest that normal β-amyloid precursor protein may serve an essential role in the maintenance of synaptic function during ageing. A compromise of this function of the β-amyloid precursor protein may contribute to the progression of the memory decline and the neurodegenerative changes seen in Alzheimer's disease.

REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L53 ANSWER 44 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:17219 HCAPLUS
DOCUMENT NUMBER: 130:163414
TITLE: Distribution of orexin receptor mRNA in the rat brain. [Erratum to document cited in CA130:76402]
AUTHOR(S): Trivedi, Prashant; Yu, Hong; MacNeil, Douglas J.; Van der Ploeg, L. H. T.; Guan, Xiao-Ming
CORPORATE SOURCE: Department of Obesity Research, Merck Research Laboratories, Rahway, NJ, 07065, USA
SOURCE: FEBS Letters (1999), 442(1), 122
CODEN: FEBLAL; ISSN: 0014-5793
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The second author was inadvertently not given the credit for having contributed equally to the study with the first author.

L53 ANSWER 45 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:812076 HCAPLUS
DOCUMENT NUMBER: 130:177667
TITLE: Molecular Interaction of Agouti Protein and Agouti-Related Protein with Human Melanocortin Receptors
AUTHOR(S): Tota, M. R.; Smith, T. S.; Mao, C.; MacNeil, T.; Mosley, R. T.; Van der Ploeg, L. H. T.; Fong, T. M.
CORPORATE SOURCE: Department of Obesity Research, Merck Research Laboratories, Rahway, NJ, 07065, USA
SOURCE: Biochemistry (1999), 38(3), 897-904
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Agouti protein and the Agouti-related protein (AGRP) are antagonists of the melanocortin-3 receptor and melanocortin-4 receptor. Both proteins contain 10 cysteines in the C-terminal domain arranged in five disulfide bonds. One possible arrangement of the disulfide bonds predicts an octapeptide loop, and the chemical properties of four residues within this loop (residues 111-114 in human AGRP) bear striking resemblance to those

of several melanocortin peptides, including α-MSH, MT-II, and SHU-9119. We showed that cyclic synthetic octapeptides based on the sequence of this loop from Agouti protein or human AGRP are functional antagonists of the human melanocortin-4 receptor. All peptides had a lower affinity for the melanocortin-3 receptor than for the melanocortin-4 receptor. Substitution of serines for cysteines resulted in linear peptides which had reduced binding affinities for both receptors. Mutational anal. of human AGRP indicated that its C-terminal domain is functionally equivalent to the intact human AGRP. The RFF111-113 triplet appears to be the most critical portion of AGRP in determining the binding affinity for both melanocortin-3 and melanocortin-4 receptors. These data strongly suggest that the loop defined by Cys-110 and Cys-117 is critical in determining the antagonist activity of human AGRP. Our data provide indirect evidence for the suggestion that the Cys-110 to Cys-117 octapeptide loop of human AGRP mimics the conformation of α-MSH, MT-II, and SHU-9119.

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L53 ANSWER 46 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:764719 HCAPLUS
DOCUMENT NUMBER: 130:76402
TITLE: Distribution of orexin receptor mRNA in the rat brain
AUTHOR(S): Trivedi, Prashant; Yu, Hong; MacNeil, Douglas J.; Van Der Ploeg, L. H. T.; Guan, Xiao-Ming
CORPORATE SOURCE: Department of Obesity Research, Merck Research Laboratories, Rahway, NJ, 07065, USA
SOURCE: FEBS Letters (1998), 438(1,2), 71-75
CODEN: FEBLAL; ISSN: 0014-5793
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The expression pattern of mRNA encoding two orexin receptors (OX1R and OX2R) in the rat brain was examined OX1R and OX2R exhibited marked differential distribution. Within the hypothalamus, OX1R mRNA is most abundant in the ventromedial hypothalamic nucleus whereas OX2R is predominantly expressed in the paraventricular nucleus. High levels of OX1R mRNA were also detected in tenia tecta, the hippocampal formation, dorsal raphe, and locus ceruleus. OX2R mRNA is mainly expressed in cerebral cortex, nucleus accumbens, subthalamic and paraventricular thalamic nuclei, anterior pretectal nucleus. The presence of orexin receptor mRNA in the hypothalamus is in support of its proposed role in feeding regulation. Broad central distribution of orexin receptors may indicate addnl. functions for orexins.

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L53 ANSWER 47 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:715925 HCAPLUS
DOCUMENT NUMBER: 129:341313
TITLE: Radiolabeled growth hormone secretagogue
INVENTOR(S): Dean, Dennis C.; Melillo, David G.; Nargund, Ravi; Van Der Ploeg, Leonardus; Pong, Sheng-Shung; Schaeffer, James M.; Smith, Roy G.
PATENT ASSIGNEE(S): Merck and Co., Inc., USA
SOURCE: U.S., 7 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5830433	A	19981103	US 1996-768368	19961217
PRIORITY APPLN. INFO.:			US 1996-768368	19961217

AB The invention is directed to [35S]-N-[1(R)-[(1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide, and pharmaceutically acceptable salts thereof. This [35S] radioligand is useful in identifying and characterizing cellular receptors which play a role in the activity of growth hormone secretatogogues. In addition, this [35S] radioligand is useful in assays which test compds. for growth hormone secretagogue activity.

REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L53 ANSWER 48 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:523050 HCAPLUS
DOCUMENT NUMBER: 129:273712
TITLE: Metabolism and function of presenilin 1
AUTHOR(S): Sisodia, S. S.; Thinakaran, G.; Wong, P. C.; Borchelt, D. R.; Lee, M. K.; Doan, A.; Regard, J.; Chen, H.; Zheng, H.; Eckman, C.; Slunt, H. H.; Ratovitsky, T.; Davenport, F.; Harris, C.; Van Der Ploeg, L. H. T.; Younkin, S. G.; Jenkins, N. A.; Copeland, N. G.; Price, D. L.
CORPORATE SOURCE: Departments of Pathology, The Johns Hopkins University School of Medicine, Baltimore, MD, USA
SOURCE: Presenilins and Alzheimer's Disease (1998), 35-47. Editor(s): Younkin, Steven G.; Tanzi, Rudolph E.; Christen, Yves. Springer: Berlin, Germany. CODEN: 66NEAP
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English

AB A review with 49 refs. Neither the normal functions of presenilins nor the mechanism(s) by which familial Alzheimer's disease (FAD)-linked mutations cause AD have been defined. Presenilin 1 (PS1) is a polytopic membrane protein that is subject to endoproteolytic processing in vivo; PS1 derivs. accumulate to saturable levels and to .apprx. 1:1 stoichiometry by mechanism(s) that are not fully defined. The authors show here that the two fragments coassemble. Moreover, the authors have detected neither interactions between PS1/PS2 and amyloid precursor protein (APP) nor influences of presenilin expression on APP maturation/secretion. To examine the in vivo function(s) of PS1, the authors developed mice with functionally inactivated PS1 alleles. These animals die before birth and exhibit several developmental defects, including a poorly differentiated vertebral column, a phenotype traced to abnormal segmentation of somites. Whole mount in situ hybridization analyses reveal that specification of somitic cell lineages is apparently unaffected, despite the clear disruption in somite segmentation. However, notable differences in expression of Notch 1 and Dll 1 mRNAs were observed in PS1-/- embryos; in contrast to wild-type embryos in which abundant expression of Notch 1 and Dll1 mRNAs are observed in the presomitic mesoderm, the expression of these genes is nearly abolished in the PS1-/- embryos. Hence, PS1 serves to regulate the spatiotemporal expression of Notch 1 and Dll1 in the paraxial mesoderm. Finally, the authors failed to detect any differences in the levels of Aβ42 and Aβ40 in brains of mice

heterozygous for PS1 relative to wild-type littermates. Thus, mutations in PS1 probably cause AD not by the loss but rather by the gain of deleterious function of mutant polypeptides.

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L53 ANSWER 49 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:398395 HCAPLUS
DOCUMENT NUMBER: 129:50499
TITLE: Mutant ob receptors and nucleotides encoding them
INVENTOR(S): Fong, Tung M.; Huang, Ruey-Ruey C.; Van Der Ploeg, Leonardus
PATENT ASSIGNEE(S): Merck & Co., Inc., USA; Fong, Tung M.; Huang, Ruey-Ruey C.; Van Der Ploeg, Leonardus
SOURCE: PCT Int. Appl., 28 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 9824881	A1	19980611	WO 1997-US22165		19971126
W: CA, JP, US					
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE					
CA 2273164	AA	19980611	CA 1997-2273164		19971126
EP 948595	A1	19991013	EP 1997-949741		19971126
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI					
JP 2001505437	T2	20010424	JP 1998-525772		19971126
US 6632625	B1	20031014	US 1997-982430		19971202
PRIORITY APPLN. INFO.:			US 1996-32367P	P	19961202
			WO 1997-US22165	W	19971126

AB Recombinant mutant ob receptors (OB-R) have been made which (a) lack a functional first CK-F3 domain Δ(41-322); (b) lack a functional second CK-F3 domain (420-496)→(500-632) or (c) lack a functional intracellular domain Δ(867-1165). The binding of the OB-R's is analyzed with 125-I leptin. Leptin response elements are linked operationally to a luciferase reporter gene to perform transactivation assay to identify novel ligands.

REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L53 ANSWER 50 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:57865 HCAPLUS
DOCUMENT NUMBER: 128:152283
TITLE: Generation of APLP2 KO mice and early postnatal lethality in APLP2/APP double KO mice
AUTHOR(S): Von Koch, C. S.; Zheng, H.; Chen, H.; Trumbauer, M.; Thinakaran, G.; Van Der Ploeg, L. H. T.; Price, D. L.; Sisodia, S. S.
CORPORATE SOURCE: Department of Neuroscience, The Johns Hopkins University School of Medicine, Baltimore, MD, 21205-2196, USA
SOURCE: Neurobiology of Aging (1997), 18(6), 661-669
CODEN: NEAGDO; ISSN: 0197-4580
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Amyloid precursor protein (APP) is a member of a larger gene family

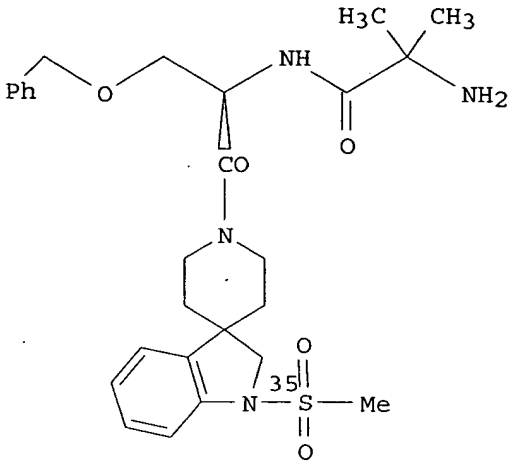
including amyloid precursor-like proteins (APLP), APLP2 and APLP1. To examine the function of APLP2 in vivo, we generated APLP2 knockout (KO) mice. They are of normal size, fertile, and appear healthy up to 22 mo of age. We observed no impaired axonal outgrowth of olfactory sensory neurons following bulbectomy, suggesting against an important role for APLP2 alone in this process. Because APLP2 and APP are highly homologous and may serve similar functions in vivo, we generated mice with targeted APLP2 and APP alleles. Approx. 80% of double KO mice die within the first week after birth, suggesting that APLP2 and APP are required for early postnatal development. The surviving .apprx.20% of double KO mice are 20-30% reduced in weight and show difficulty in righting, ataxia, spinning behavior, and a head tilt, suggesting a deficit in balance and/or strength. Adult double KO mice mate poorly, despite apparent normal ovarian and testicular development. Otherwise, double KO mice appear healthy up to 13 mo of age. We conclude, that APLP2 and APP can substitute for each other functionally.

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L53 ANSWER 51 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:501501 HCAPLUS
DOCUMENT NUMBER: 127:106081
TITLE: Radiolabeled growth hormone secretagogue
INVENTOR(S): Dean, Dennis C.; Melillo, David G.; Nargund, Ravi; Van Der Ploeg, Leonardus; Pong, Sheng-Shung; Schaeffer, James M.; Smith, Roy G.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA; Dean, Dennis C.; Melillo, David G.; Nargund, Ravi; Van Der Ploeg, Leonardus; Pong, Sheng-Shung; Schaeffer, James M.; Smith, Roy G.
SOURCE: PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9722367	A1	19970626	WO 1996-US20007	19961216

W: CA, JP, US
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
PRIORITY APPLN. INFO.: US 1995-8961P P 19951220
GI



I

AB The present invention is directed to [35S]-N-[1(R)-[1(R)-(1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethoxy)ethyl]-2-amino-2-methylpropanamide (I), and pharmaceutically acceptable salts thereof. This [35S] radioligand is useful in identifying and characterizing cellular receptors which play a role in the activity of growth hormone secretagogues. In addition, this [35S] radioligand is useful in assays which test compds. for growth hormone secretagogue activity.

L53 ANSWER 52 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:282140 HCAPLUS
DOCUMENT NUMBER: 127:603
TITLE: Repeat administration of the GH secretagogue MK-0677 increases and maintains elevated IGF-I levels in beagles
AUTHOR(S): Hickey, G. J.; Jacks, T. M.; Schleim, K.-D.; Frazier, E.; Chen, H. Y.; Krupa, D.; Feeney, W.; Nargund, R. P.; Patchett, A. A.; Smith, R. G.
CORPORATE SOURCE: Departments of Physiology and Biochemistry, Merck Res. Laboratories, Rahway, NJ, USA
SOURCE: Journal of Endocrinology (1997), 152(2), 183-192
CODEN: JOENAK; ISSN: 0022-0795
PUBLISHER: Journal of Endocrinology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We have reported that MK-0677 is a novel, orally active GH secretagogue that stimulates an immediate and long-lasting increase in serum GH levels in dogs. Significant elevations in IGF-I levels were associated with the increased GH secretion. Cortisol secretion was also increased following MK-0677 administration. In the current study, we determined the effect of repeat oral administration of MK-0677 on GH, IGF-I and cortisol levels; we also investigated if the GH and cortisol responses to MK-0677 are influenced by circulating IGF-I concns. Following the initial oral administration of MK-0677, GH secretion (area under the time-response curve (AUC) ng/mL per h) was increased 7.9- to 9.8-fold (1.0 mg/kg), 5.6-fold (0.5 mg/kg) or 3.9-fold (0.25 mg/kg). With repeat MK-0677 administration, the GH response was decreased by 41-77%; GH concns. remained significantly above control in the 0.5 mg/kg and 1.0 mg/kg groups. Individual beagle GH profiles indicated that the increased GH concentration was associated with an amplified GH pulsatile profile. Serum IGF-I

levels were significantly increased over control levels at all dosage levels by 480 min on the first day of MK-0677 administration. With repeated administration, IGF-I levels were increased up to 126% and remained elevated through 14 days, the longest treatment period evaluated. While daily MK-0677 administration appeared to increase IGF-1 levels over 24 h, as evidenced by significant increases in the pretreatment IGF-I levels on days 4-14, no such increase was noted with alternate day MK-0677 administration; thus the dosage regimen modulated circulating IGF-I levels. MK-0677 stimulated increases in cortisol secretion (AUC μg/dL per h) on the first day of treatment. A decreased cortisol response was observed following repeated daily treatment with MK-0677; in contrast, with alternate day treatment, no decrease in cortisol response to MK-0677 occurred. A marked increase in circulating IGF-I concns. following administration of exogenous GH resulted in a significant decrease in both the GH and cortisol response to MK-0677 compared with control animals. Our findings suggested, therefore, that circulating IGF-I concns. regulate GH and cortisol response to MK-0677. In summary, chronic and administration of MK-0677 was associated with significant increases in GH and IGF-I levels that were maintained for the duration of the treatment. The GH profile following MK-0677 administration consisted of episodic increases above control. Compared with day 1, repeated daily treatment with MK-0677 resulted in an attenuated GH response that was associated with an increase in circulating IGF-I levels. The cortisol response was similarly reduced during chronic MK-0677 treatment, suggesting that IGF-I mediated neg. feedback on both the GH and cortisol axes. The fact that similar attenuation of the GH and cortisol responses to MK-0677 on day 1 was observed if IGF-I levels were increased by treating animals with exogenous GH suggested that the attenuated response to MK-0677 that occurred during chronic treatment was mediated by increases in IGF-I rather than desensitization to MK-0677. Thus, a regulatory feedback loop apparently prevents hyperstimulation of the GH axis by MK-0677. We conclude that MK-9677 offers the potential of an orally active GH secretagogue that can maintain elevated IGF-I levels when administered chronically.

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L53 ANSWER 53 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1996:725433 HCAPLUS
DOCUMENT NUMBER: 126:69945
TITLE: MK-0677, a potent, novel, orally active growth hormone (GH) secretagogue: GH, insulin-like growth factor I, and other hormonal responses in beagles
AUTHOR(S): Jacks, Thomas; Smith, Roy; Judith, Fred; Schleim, Klaus; Frazier, Easter; Chen, Howard; Krupa, David; Hora, Don, Jr.; Nargund, Ravi; et al.
CORPORATE SOURCE: Department Physiology and Biochemistry, Merck Research Laboratories, Rahway, NJ, 07065, USA
SOURCE: Endocrinology (1996), 137(12), 5284-5289
CODEN: ENDOAO; ISSN: 0013-7227
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB MK-0677, a spiroindoline sulfonamide, is a novel, orally active GH secretagogue. The effects of MK-0677 on serum GH and other hormones after oral and i.v. single dose administrations in beagles were evaluated. After oral administration in a balanced eight-dog cross-over study, treatment with MK-0677 significantly increased peak GH concns., with a 5.3-fold increase (mean, 10.5 ng/mL) at the 0.25 mg/kg dose, a 9.0-fold increase (18.0 ng/mL) at the 0.50 mg/kg dose, and a 15.8-fold increase

(31.6 ng/mL) at the 1.0 mg/kg dose. Total GH release, expressed as the area under the curve, showed similar significant increases over the effect of the water placebo. A single oral 1 mg/kg dose in three dogs induced a mean GH peak of 27.6 ± 1.5 ng/mL at 120 min, and GH levels remained elevated up to 360 min after treatment. Insulin-like growth factor I (IGF-I) levels were significantly increased by 30% at 480 min after treatment. Cortisol levels were increased 2.4-fold over pretreatment levels. After i.v. administration, compared to the saline control group which had a mean serum GH peak of 3.8 ng/mL, MK-0677 at 0.25 mg/kg significantly increased peak GH concns. 20.4-fold (77.4 ng/mL). Total GH release, expressed as the area under the curve, showed a similar increase. The mean peak GH level was recorded 10 min after treatment, with GH levels elevated up to 180 min after treatment. IGF-I levels were significantly elevated by 25% at 360 min after the administration of MK-0677. Cortisol levels were increased 2.3-fold over pretreatment levels. Insulin and glucose levels were higher, LH and PRL levels were unaltered, and T4 levels were marginally lower; the levels of each of these hormones remained within the normal ranges for dogs throughout the experiment In summary, MK-0677 is a potent GH secretagogue that induces an immediate, large, long-lasting increase in GH levels when administered orally or i.v. In contrast to GH-releasing peptide-6 and benzolactam secretagogues, GH levels were elevated up to 360 min after treatment, and this was associated with a significant increase in IGF-I levels. Cortisol levels were increased; however, the increases were modest compared to those in GH.

REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L53 ANSWER 54 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:665073 HCAPLUS
DOCUMENT NUMBER: 125:318039
TITLE: Growth hormone (GH) and insulin-like growth factor I responses after treatments with an orally active GH secretagogue L-163,255 in swine
AUTHOR(S): Chang, C. H.; Rickes, E. L.; McGuire, L.; Frazier, E.; Chen, H.; Barakat, K.; Nargund, R.; Patchett, A.; Smith, R. G.; Hickey, G. J.
CORPORATE SOURCE: Department Biochemistry Physiology Medicinal Chemistry, Merck Research Laboratories, Rahway, NJ, 07065-0900, USA
SOURCE: Endocrinology (1996), 137(11), 4851-4856
CODEN: ENDOAO; ISSN: 0013-7227
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB L-163,255 is a potent orally active spiropiperidine GH secretagogue. When administered i.v. or orally, L-163,255 caused GH to be increased in a dose-related manner, with a return to baseline by 90 min. After i.v. administrations of saline and L-163,255 at 1, 3, and 10 μg/kg, GH areas under the curves (GH AUCs) over 120 min were 377, 1151, 795, and 1770 ng/min/mL, and peak GH concns. were 8,16, 17 and 43 ng/mL, resp. No changes in plasma cortisol concns. were noted. After oral administrations at 3, 10, and 30 μg/kg, GH AUCs over 180 min were 1133, 1246, and 1551 ng/min/mL, peak GH concns. were 7,11, and 23 ng/mL, resp. After administration in feed, L-163,255 caused a dose-related increase in GH, with an initial peak observed at 60 min for both 30 and 300 μg/kg dose groups, and remained elevated above baseline through 180 min for the high dose group only. GH AUCs for 180 min posttreatment were 929 and 1897 ng/min/mL, and peak GH concns. were 9 and 22 ng/mL for the 30 and 300 μg/kg doses prepared in 150 g feed, resp. When provided in feed ad libitum over the 72-h period, mean plasma insulin-like growth factor I

levels increased 15%, 62%, and 109% in the untreated, treated with L-163,255 at 360 ppm, or treated with porcine somatotropin groups, resp. Repeated i.v. administration of L-163,255 at 1 mg/kg once daily over 14 days resulted in an initial marked GH response, followed by a much reduced, but significantly elevated, GH response over the saline control values on subsequent treatment days. Repeated i.v. treatments with L-163,255 also resulted in an elevated insulin-like growth factor I level (.apprx.60%) over that in saline controls. Compared to those in saline controls, plasma cortisol concns. tended to be increased after the initial dose of L-163,255, but no significant increases were noted on days 7 and 14 in the L-163,255 group. The results of these studies indicate that L-163,255 is an orally active GH secretagogue suitable for long term efficacy studies in swine.

L53 ANSWER 55 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:483721 HCAPLUS
DOCUMENT NUMBER: 125:134812
TITLE: Transgenic animal lacking native amyloid precursor protein
INVENTOR(S): Zheng, Hui; Chen, Howard Y.; Trumbauer, Myrna E.; Van Der Ploeg, Leonardus H. T.
PATENT ASSIGNEE(S): Merck and Co., Inc., USA
SOURCE: PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9617926	A1	19960613	WO 1995-US15672	19951201
W: CA, JP, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2206789	AA	19960613	CA 1995-2206789	19951201
EP 799305	A1	19971008	EP 1995-942534	19951201
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE				
JP 2000504202	T2	20000411	JP 1996-517675	19951201
US 6187992	B1	20010213	US 1999-266475	19990311
PRIORITY APPLN. INFO.:			US 1994-349334 A1	19941205
			WO 1995-US15672 W	19951201
			US 1997-849487 B2	19970605

AB A transgenic nonhuman animal lacking native amyloid precursor protein (APP) is disclosed. A mouse APP cosmid clone was used for the preparation of a replacement vector pHZ038 which deletes a 3.8-kb sequence comprising the 1.0-kb APP promoter, the first exon, and part of the first intron. Targeted recombination between the vector and the wild-type APP locus results in the deletion of the promoter an exon 1 of the APP gene followed by its replacement with a 1.5-kb neo coding sequence. Thus, embryonic stem cells containing the altered APP gene are injected into mouse blastocysts, and transplanted into pseudopregnant mouse to produce a founder transgenic mouse. Homozygous APP knockout mice that result appeared normal and healthy up to 14 wk of age but do not produce APP mRNA as shown by Northern anal. of RNA isolated from brain; the APP mRNA level was reduced by .apprx.50% in heterozygous mice as compared to wild-type controls. The transgenic mouse may be used in the study of Alzheimer's Disease and disorders involving the central nervous system.

L53 ANSWER 56 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:440973 HCAPLUS

DOCUMENT NUMBER: 125:82497
TITLE: Cloning of cDNA for para cation channel of Drosophila and functional expression with tipE
INVENTOR(S): Liu, Ken; Van Der Ploeg, Leonardus H. T.; Wang, Peiyi; Warmke, Jeffrey W.; Arena, Joseph P.; Hall, Linda M.; Feng, Guoping
PATENT ASSIGNEE(S): Merck and Co., Inc., USA; State University of New York At Buffalo
SOURCE: PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9615220	A1	19960523	WO 1995-US14378	19951106
W: CA, JP, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5593864	A	19970114	US 1994-337339	19941110
CA 2204770	AA	19960523	CA 1995-2204770	19951106
EP 789753	A1	19970820	EP 1995-940621	19951106
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
JP 10508752	T2	19980902	JP 1995-516147	19951106
US 5688917	A	19971118	US 1996-724095	19960930
PRIORITY APPLN. INFO.:			US 1994-337339	A1 19941110
			WO 1995-US14378	W 19951106

AB Drosophila DNAs encoding voltage-activated cation channels, para (α subunit) and tipE (β subunit), have been cloned and characterized. The cDNAs have been co-expressed in recombinant host cells (e.g. Xenopus oocytes) which produce active recombinant protein. The recombinant protein is also purified from the recombinant host cells.

L53 ANSWER 57 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:435233 HCAPLUS
DOCUMENT NUMBER: 125:79425
TITLE: Drosophila gene para voltage-activated sodium channel α-subunit cDNA sequence, protein recombinant expression, channel modulator identification, and insecticide or arachnicidic agent
INVENTOR(S): Van Der Ploeg, Leonardus H. T.; Warmke, Jeffrey W.
PATENT ASSIGNEE(S): Merck and Co., Inc., USA
SOURCE: PCT Int. Appl., 55 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9614860	A1	19960523	WO 1995-US14262	19951106
W: CA, JP, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5550049	A	19960827	US 1994-338702	19941110
CA 2204849	AA	19960523	CA 1995-2204849	19951106
EP 790833	A1	19970827	EP 1995-939727	19951106
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				

JP 10508751	T2	19980902	JP 1995-516133	19951106
US 7001734	B1	20060221	US 1995-554424	19951106
PRIORITY APPLN. INFO.:			US 1994-338702	A1 19941110
			WO 1995-US14262	W 19951106

AB DNAs encoding voltage-activated cation channels have been cloned and characterized. The cDNA's have been expressed in recombinant host cells which produce active recombinant protein. The recombinant protein is also purified from the recombinant host cells. In addition, the recombinant host cells are utilized to establish a method for identifying modulators of the channel activity, and channel modulators are identified. Channel modulators are useful as insecticides and arachnicidic agents.

L53 ANSWER 58 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:397343 HCAPLUS
DOCUMENT NUMBER: 125:50785
TITLE: Inactivated interleukin-1β-encoding gene and production of interleukin-1β-deficient transgenic animal, especially using embryo stem cell and mouse host
INVENTOR(S): Chen, Howard Y.; Hofmann, Kathryn J.; Van der Ploeg, Leonardus H. T.; Trumbauer, Myrna E.; Zheng, Hui
PATENT ASSIGNEE(S): Merck and Co., Inc., USA
SOURCE: PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9612792	A1	19960502	WO 1995-US13341	19951016
W: CA, JP, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2202991	AA	19960502	CA 1995-2202991	19951016
EP 787179	A1	19970806	EP 1995-938264	19951016
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
JP 10507637	T2	19980728	JP 1995-514033	19951016
PRIORITY APPLN. INFO.:			US 1994-326431	A 19941020
			WO 1995-US13341	W 19951016

AB A transgenic animal with alterations in an IL-1β gene is prepared by introduction of a gene encoding an altered IL-1β gene into a host animal. Altered embryo stem cells, blastocyst microinjection, pseudopregnant mouse transplants, and breeding to produce heterozygous or homozygous animals are included. Interleukin-1β-deficient transgenic animals model chronic or acute inflammation.

L53 ANSWER 59 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:328642 HCAPLUS
DOCUMENT NUMBER: 125:7575
TITLE: Transgenic animal expressing a familial form of human amyloid precursor protein as a model for Alzheimer's disease
INVENTOR(S): Singh, Gurparkash; Chen, Howard Y.; Heavens, Robert P.; Sirinathsinghji, Dalip J. S.; Smith, David W.; Trumbauer, Myrna E.; Van Der Ploeg, Leonardus H. T.; Vongs, Aurawan; Zheng, Hui
PATENT ASSIGNEE(S): Merck and Co., Inc., USA
SOURCE: PCT Int. Appl., 35 pp.

CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9606927	A1	19960307	WO 1995-US10920	19950828
W: CA, JP, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2198451	AA	19960307	CA 1995-2198451	19950828
EP 778886	A1	19970618	EP 1995-932340	19950828
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
JP 10504964	T2	19980519	JP 1995-508912	19950828
US 6211428	B1	20010403	US 1997-793558	19970428
PRIORITY APPLN. INFO.:			US 1994-299872 A	19940901
			WO 1995-US10920 W	19950828

AB Transgenic mice with the gene for human amyloid precursor protein (APP751 with substitution of Val698 substituted by Ile) associated with familial Alzheimer's disease under control of the neuron-specific Thy-1 promoter are described for use as models of Alzheimer's disease. The transgenic mice may be used to evaluate compds. affecting Alzheimer's disease and other cognitive disorders.

L53 ANSWER 60 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:8901 HCAPLUS
DOCUMENT NUMBER: 124:46081
TITLE: Induction of c-fos mRNA in the arcuate nucleus of normal and mutant growth hormone-deficient mice by a synthetic non-peptidyl growth hormone secretagogue
AUTHOR(S): Sirinathsinghji, D. J. S.; Chen, H. Y.; Hopkins, R.; Trumbauer, M.; Heavens, R.; Rigby, M.; Smith, R. G.; Van der Ploeg, L. H. T.
CORPORATE SOURCE: Merck Sharp and Dohme Research Laboratories, Neuroscience Research Centre, Harlow Essex, CM20 2QR, UK
SOURCE: NeuroReport (1995), 6(15), 1989-92
CODEN: NERPEZ; ISSN: 0959-4965
PUBLISHER: Rapid Science Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors have studied by in situ hybridization histochem. the mRNA expression of the c-fos immediate early gene in the brains of wild type and dwarf (dw/dw) and little (lit/lit) mutant-mice after systemic injections of the synthetic GH secretagogues GHRP-6 and L-163,191. Both GH secretagogues induced a marked c-fos mRNA expression in the arcuate-ventromedial hypothalamus (ARC-VMH) of both control and mutant mice indicating a possible action on growth hormone releasing hormone (GHRH) neurons in the ARC-VMH. Both dw/dw and lit/lit mice showed a 5-fold elevation in GHRH mRNA expression in the ARC-VMH compared with control animals under basal conditions. Since lit/lit mice have a reduced ability to secrete GH and lack a functional GHRH receptor while dw/dw mice lack both GH and presumably GHRH receptors, the GH-secretagogue-induced c-fos mRNA in the brain of these mutants are unlikely to be mediated by an indirect action of GH or a interaction of the synthetic GH-secretagogue with the GHRH receptor.

L53 ANSWER 61 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1995:513685 HCAPLUS

DOCUMENT NUMBER: 122:262955
TITLE: Transgenic animals expressing a human interleukin 1β gene as a model for cognitive disorders
INVENTOR(S): Chen, Howard Y.; Hofmann, Kathryn J.; van der Ploeg, Lenonardus H. T.; Shaw, Alan R.; Trumbauer, Myrna E.; Zheng, Hui
PATENT ASSIGNEE(S): Merck and Co., Inc., USA
SOURCE: PCT Int. Appl., 21 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 9503397	A1	19950202	WO 1994-US8110		19940719
W: CA, JP, US					
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE					
CA 2167581	AA	19950202	CA 1994-2167581		19940719
EP 724628	A1	19960807	EP 1994-922619		19940719
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE					
JP 09500533	T2	19970121	JP 1994-505260		19940719
PRIORITY APPLN. INFO.:			US 1993-96944	A	19930722
			WO 1994-US8110	W	19940719

AB Transgenic mice expressing the human interleukin 1β gene are constructed for use in the evaluation of compds. affecting Alzheimer's disease and other cognitive disorders. The transgene is placed under control of the Thy-1 promoter to limit expression to neural tissue. Construction of the expression cassette and its introduction into mouse embryo by microinjection are described.

L53 ANSWER 62 OF 62 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1995:511595 HCAPLUS
DOCUMENT NUMBER: 122:263538
TITLE: Expression of the human interleukin-1β gene in a transgenic animal
INVENTOR(S): Chen, Howard Y.; Hofmann, Kathryn J.; Van Der Ploeg, Leonardus H. T.; Shaw, Alan R.; Trumbauer, Myrna E.; Zheng, Hui
PATENT ASSIGNEE(S): Merck and Co., Inc., USA
SOURCE: PCT Int. Appl., 24 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 9503402	A1	19950202	WO 1994-US8111		19940719
W: CA, JP, US					
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE					
CA 2167580	AA	19950202	CA 1994-2167580		19940719
EP 710283	A1	19960508	EP 1994-923543		19940719
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE					
JP 09500534	T2	19970121	JP 1995-505261		19940719
US 5824837	A	19981020	US 1996-571983		19960422
PRIORITY APPLN. INFO.:			US 1993-96943	A	19930722
			WO 1994-US8111	W	19940719

AB Transgenic non-human animals with a human interleukin-1β gene under control of the murine metallothionein-1 promoter are provided. The transgenic animals and cell cultured derived from them may be used to study inflammation and cognitive disorders. The construction of the expression vector and the preparation of transgenic mice by microinjection of embryos are described. Transgenic mice were identified by screening for a sequence from SV40 present on the transforming DNA.

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